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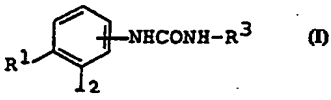
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶: C07D 209/08, A61K 31/33, 31/17, C07D 403/12, 401/12, 405/12, C07C 327/48, 327/58, 275/58	A1	(11) International Publication Number: WO 96/39382 (43) International Publication Date: 12 December 1996 (12.12.96)
(21) International Application Number: PCT/JP96/01500 (22) International Filing Date: 4 June 1996 (04.06.96) (30) Priority Data: 9511355.1 6 June 1995 (06.06.95) GB (71) Applicant (for all designated States except US): FUJISAWA PHARMACEUTICAL CO., LTD. [JP/JP]; 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541 (JP). (72) Inventors; and (75) Inventors/Applicants (for US only): ITO, Kiyotaka [JP/JP]; 1279-207, Higashifutami, Futami-cho, Akashi-shi, Hyogo 674 (JP). SPEARS, Glen, W. [US/JP]; 2-2-13-101, Midori-gaoka, Ikeda-shi, Osaka 563 (JP). YAMANAKA, Toshio [JP/JP]; 1-4-5, Akagawa, Asahi-ku, Osaka-shi, Osaka 535 (JP). HARADA, Keiko [JP/JP]; 1-2-10-203, Nakasujiyama, Takarazuka-shi, Hyogo 665 (JP). HOTTA, Yuka [JP/JP]; 1-21-14, Mefu, Takarazuka-shi, Hyogo 665 (JP). KATO, Masayuki [JP/JP]; 6-16-12, Goryo-oeyamacho, Nishikyo-ku, Kyoto-shi, Kyoto 610-11 (JP).		(74) Agent: SEKI, Hideo; Fujisawa Pharmaceutical Co., Ltd., Osaka Factory, 1-6, Kashima 2-chome, Yodogawa-ku, Osaka-shi, Osaka 532 (JP). (81) Designated States: CA, CN, JP, KR, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
(54) Title: UREA DERIVATIVES AS 5-HT ANTAGONISTS (57) Abstract <p>A compound of formula (I) wherein R¹ is cyano, thiocarbamoyl, a group of formula (a) in which R⁴ is hydrogen, lower alkyl which may have optionally substituted aryl, acyl, optionally substituted aryl, lower alkylthio or 1-lower alkylindolyl, A¹ is lower alkylene, and m and n are each 0 or 1, a group of the formula -A²-R⁵ in which R⁵ is morpholino, piperidino, 4-arylpiperazin-1-yl, phthalimido, 1,2,3,4-tetrahydroquinolin-1-yl, 1,2,3,4-tetrahydroisoquinolin-2-yl or imidazol-1-yl, and A² is lower alkylene, or a group of formula (b) in which R⁶ and R⁷ are each hydrogen, optionally substituted aryl, acyl, pyridyl(lower)alkyl, thienyl(lower)alkyl, 3,4-dihydroisoquinolinyl, (lower alkylimino) (optionally substituted aryl) methyl or lower alkyl which may have optionally substituted aryl, and A³ is lower alkylene, and R² is hydrogen; or R¹ and R² are linked together to form (1), (2), or (3), in which R⁸ is amino or acylamino, and R⁹ is hydrogen, acyl or lower alkyl which may have optionally substituted aryl, and R³ is 1-lower alkylindolyl, benzofuranyl, dihydrobenzofuranyl, or optionally substituted aryl, and a pharmaceutically acceptable salt thereof, which is useful as a medicament for prophylactic and therapeutic treatment of 5-HT mediated diseases.</p> <div style="text-align: right; margin-top: 20px;">  <p style="text-align: right;">(I)</p> </div> <div style="text-align: right; margin-top: 20px;"> $-(A^1-NH)_m-\overset{NH}{\underset{ }{C}}-(NH)_n-R^4 \quad (a)$ </div> <div style="text-align: right; margin-top: 20px;"> $-A^3-\overset{R^6}{\underset{ }{N}}-R^7 \quad (b)$ </div> <div style="text-align: right; margin-top: 20px;"> $-(CH_2)_3-\underset{\underset{R^8}{ }}{CH}- \quad (1)$ </div> <div style="text-align: right; margin-top: 20px;"> $-(CH_2)_2-\underset{\underset{R^9}{ }}{N}-CH_2- \quad (2)$ </div> <div style="text-align: right; margin-top: 20px;"> $-(CH_2)_3-\underset{\underset{R^9}{ }}{N}- \quad (3)$ </div>		

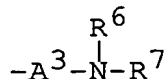
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a group of the formula :

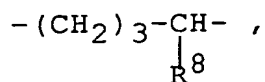


5 in which R⁶ and R⁷ are each hydrogen, optionally substituted aryl, acyl, pyridyl(lower)alkyl, thienyl(lower)alkyl, 3,4-dihydroisoquinoliny, (lower alkylimino) (optionally substituted aryl) 10 methyl or lower alkyl which may have optionally substituted aryl, and

A³ is lower alkylene, and

R² is hydrogen; or

15 R¹ and R² are linked together to form



20 $-(\text{CH}_2)_2-\text{N}-\text{CH}_2-$, or
 $\begin{array}{c} | \\ \text{R}^9 \end{array}$

25 $-(\text{CH}_2)_3-\text{N}-$,
 $\begin{array}{c} | \\ \text{R}^9 \end{array}$

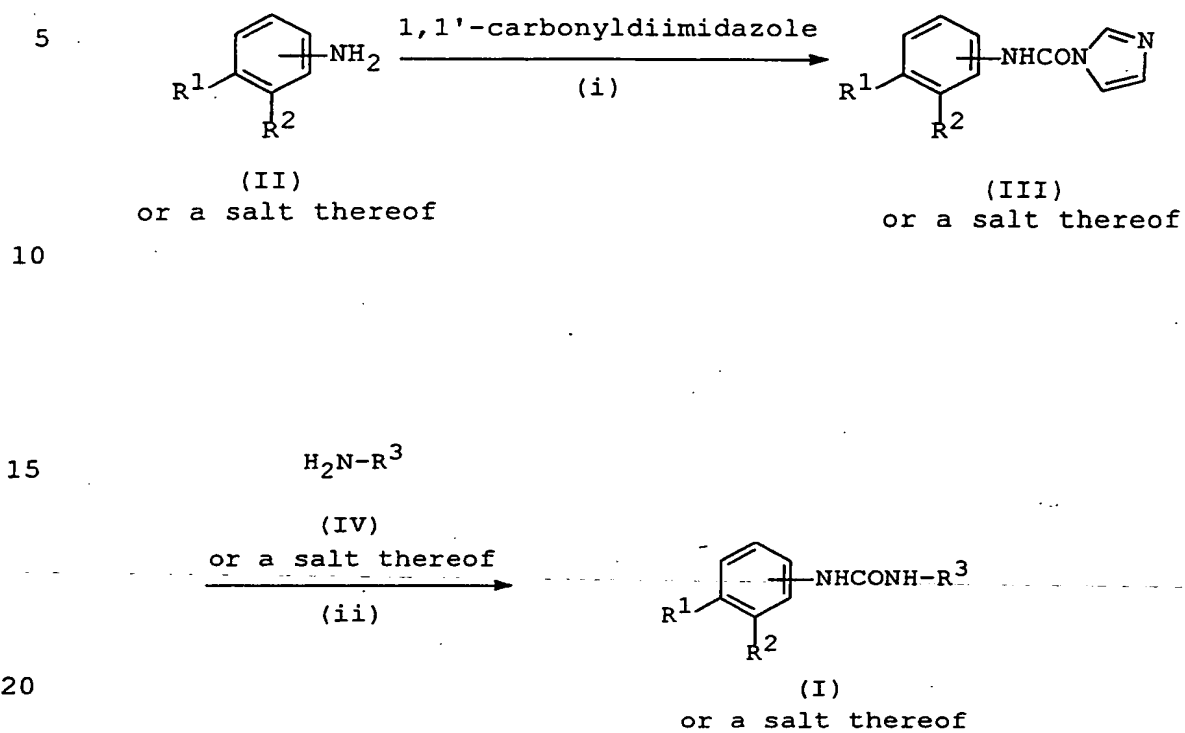
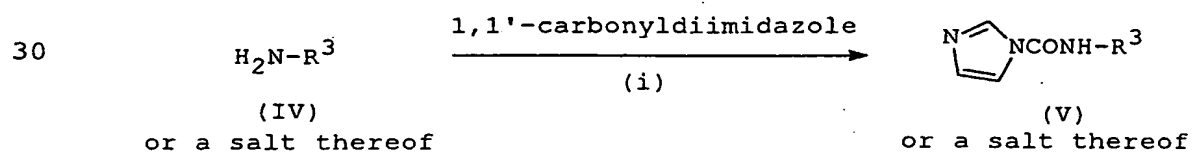
in which R⁸ is amino or acylamino, and

R⁹ is hydrogen, acyl or lower alkyl which may have optionally substituted aryl, and

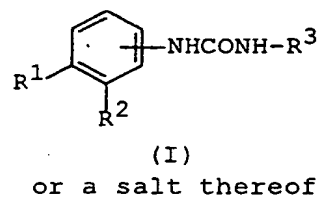
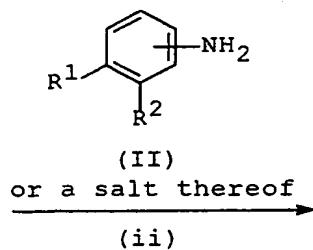
30 R³ is 1-lower alkylindolyl, benzofuranyl, dihydrobenzofuranyl, or optionally substituted aryl.

According to the present invention, the object compounds
 35 (I) can be prepared by the following main processes :

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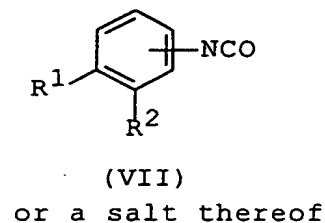
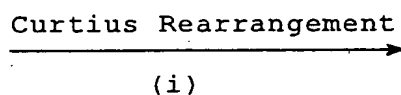
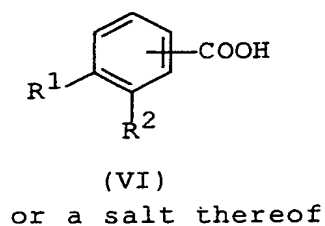
Process 1Process 2

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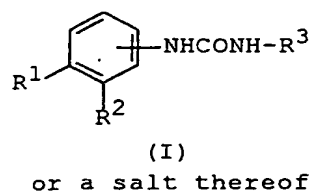
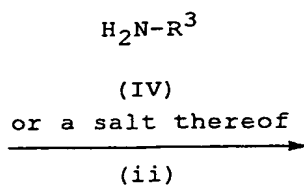


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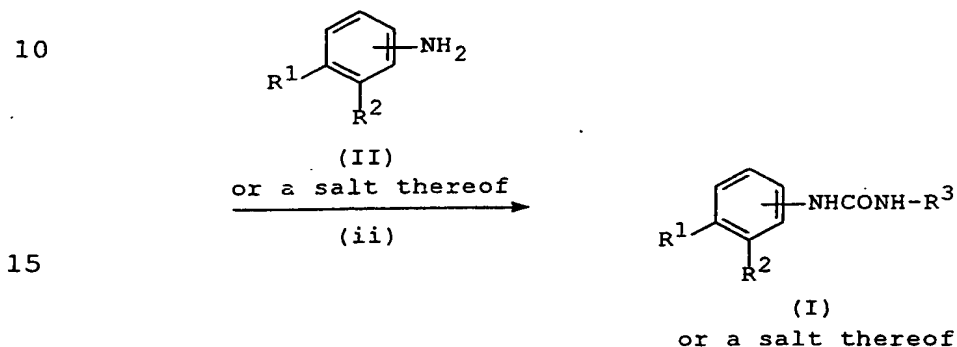
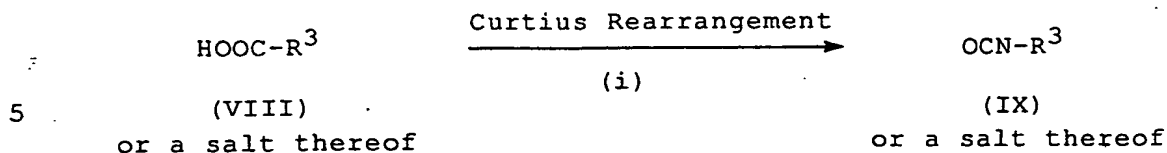
Process 3

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Process 4

20

wherein R^1 , R^2 and R^3 are each as defined above.

25 Further, the object compounds (I) prepared by the above Processes 1 to 4 can be achieved conversion of their side chain within the scope of the compounds of the present invention as shown in the Examples below.

30 Suitable salt of the compounds (I), (II), (III), (IV), (V), (VI), (VII), (VIII) and (IX) are conventional non-toxic pharmaceutically acceptable salt and may include a salt with a base or an acid addition salt such as a salt with an inorganic base, for example, an alkali metal salt (e.g. sodium salt, potassium salt, cesium salt, etc.), an alkaline

35 earth metal salt (e.g. calcium salt, magnesium salt, etc.),

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an ammonium salt; a salt with an organic base, for example, an organic amine salt (e.g. triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.), etc.; an inorganic acid addition salt (e.g. hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, etc.); an organic carboxylic or sulfonic acid addition salt (e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, p-toluenesulfonate, etc.); a salt with a basic or acidic amino acid (e.g. arginine, aspartic acid, glutamic acid, etc.); and the like, and the preferable example thereof is an acid addition salt.

In the above and subsequent descriptions of the present specification, suitable examples and illustrations of the various definitions which the present invention include within the scope thereof are explained in detail as follows.

The term "lower" is intended to mean 1 to 6 carbon atoms, preferably 1 to 4 carbon atoms, unless otherwise indicated.

Suitable "lower alkyl" and lower alkyl moiety in the term "lower alkylthio", "1-lower alkylindolyl", "pyridyl(lower)alkyl" and "thienyl(lower)alkyl" may include straight or branched one, having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl, preferably one having 1 to 4 carbon atoms, and the like, in which the most preferred one is methyl, ethyl, propyl or butyl.

Suitable "lower alkylene" is one having 1 to 6 carbon atom(s) and may include methylene, ethylene, methylenemethylene, trimethylene, propylene, tetramethylene, methyltrimethylene, hexamethylene, and the like, in which the preferred one is methylene or methylenemethylene.

Suitable "optionally substituted aryl" includes aryl

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(e.g. phenyl, naphthyl, etc.) which may have suitable substituent(s) such as lower alkyl as mentioned above, lower alkoxy (e.g. methoxy, ethoxy, propoxy, etc.), halogen (e.g. fluoro, chloro, bromo, etc.), trihalo(lower)alkoxy (e.g. trifluoromethoxy, etc.), N,N-di(lower alkyl)amino (e.g. N,N-dimethylamino, etc.), and the like.

"lower alkyl which may have optionally substituted aryl" means lower alkyl as mentioned above, which may have optionally substituted aryl as mentioned above.

Suitable "4-arylpiperazin-1-yl" may include 4-phenylpiperazin-1-yl, 4-naphthylpiperazin-1-yl, and the like.

Suitable "(lower alkylimino) (optionally substituted aryl)methyl" may include (methylimino) (phenyl)methyl, and the like.

Suitable "acyl" and "acyl moiety" in the terms "acylamino" may include carbamoyl, aliphatic acyl group and acyl group containing an aromatic ring, which is referred to as aromatic acyl, or heterocyclic ring, which is referred to as heterocyclic acyl.

Suitable example of said acyl may be illustrated as follows :

Carbamoyl; Thiocarbamoyl;

Aliphatic acyl such as lower or higher alkanoyl (e.g., formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-dimethylpropanoyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl, undecanoyl, dodecanoyl, tridecanoyl, tetradecanoyl, pentadecanoyl, hexadecanoyl, heptadecanoyl, octadecanoyl, nonadecanoyl, icosanoyl, etc.); lower or higher alkoxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl, t-pentyloxycarbonyl, heptyloxycarbonyl, etc.); lower or higher alkylsulfonyl (e.g., methylsulfonyl,

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ethylsulfonyl, etc.);

lower or higher alkoxysulfonyl (e.g., methoxysulfonyl, ethoxysulfonyl, etc.);

5 cyclo(lower)alkylcarbonyl (e.g., cyclopentylcarbonyl, cyclohexylcarbonyl, etc.); or the like;

Aromatic acyl such as

aroyl (e.g., benzoyl, toluoyl, naphthoyl, etc.);

10 ar(lower)alkanoyl [e.g., phenyl(lower)alkanoyl (e.g., phenylacetyl, phenylpropanoyl, phenylbutanoyl, phenylisobutanoyl, phenylpentanoyl, phenylhexanoyl, etc.), naphthyl(lower)alkanoyl (e.g., naphthylacetyl, naphthylpropanoyl, naphthylbutanoyl, etc.), etc.];

15 ar(lower)alkenoyl [e.g., phenyl(lower)alkenoyl (e.g., phenylpropenoyl, phenylbutenoyl, phenylmethacryloyl, phenylpentenoyl, phenylhexenoyl, etc.), naphthyl(lower)alkenoyl (e.g., naphthylpropenoyl, naphthylbutenoyl, etc.), etc.];

20 ar(lower)alkoxycarbonyl [e.g., phenyl(lower)alkoxycarbonyl (e.g., benzyloxycarbonyl, etc.), etc.]; aryloxycarbonyl (e.g., phenoxycarbonyl, naphthyloxycarbonyl, etc.);

aryloxy(lower)alkanoyl (e.g., phenoxyacetyl, phenoxypropionyl, etc.);

25 arylglyoxyloyl (e.g., phenylglyoxyloyl, naphthylglyoxyloyl, etc.);

arylsulfonyl (e.g., phenylsulfonyl, p-tolylsulfonyl, etc.); or the like;

Heterocyclic acyl such as

heterocycliccarbonyl;

30 heterocyclic(lower)alkanoyl (e.g., heterocyclicacetyl, heterocyclicpropanoyl, heterocyclicbutanoyl, heterocyclicpentanoyl, heterocyclichexanoyl, etc.);

35 heterocyclic(lower)alkenoyl (e.g., heterocyclicpropenoyl, heterocyclicbutenoyl, heterocyclicpentenoyl, heterocyclichexenoyl, etc.);

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heterocyclicglyoxyloyl; or the like;
in which suitable "heterocyclic moiety" in the terms
"heterocycliccarbonyl", "heterocyclic(lower)alkanoyl",
heterocyclic(lower)alkenoyl" and "heterocyclicglyoxyloyl" as
5 mentioned above means, in more detail, saturated or
unsaturated, monocyclic or polycyclic heterocyclic group
containing at least one hetero-atom such as an oxygen,
sulfur, nitrogen atom and the like.

And, especially preferable heterocyclic group may be
10 heterocyclic group such as

unsaturated 3 to 8-membered (more preferably 5 or 6-
membered) heteromonocyclic group containing 1 to 4 nitrogen
atom(s), for example, pyrrolyl, pyrrolinyl, imidazolyl,
pyrazolyl, pyridyl, dihydropyridyl, pyrimidinyl, pyrazinyl,
15 pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,4-
triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.),
tetrazolyl (e.g., 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.;

saturated 3 to 8-membered (more preferably 5 or 6-
membered) heteromonocyclic group containing 1 to 4 nitrogen
20 atom(s), for example, pyrrolidinyl, imidazolidinyl,
piperidyl, piperazinyl, etc.;

unsaturated condensed heterocyclic group containing 1 to
4 nitrogen atom(s), for example, indolyl, isoindolyl,
indolinyl, indolizinyl, benzimidazolyl (e.g. 1H-
25 benzimidazolyl, etc.), quinolyl, isoquinolyl,
tetrahydroisoquinolyl (e.g. 1,2,3,4-tetrahydroisoquinolyl,
etc.) indazolyl, benzotriazolyl, quinazolinyl, quinoxalinyl,
phthalazinyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-
30 membered) heteromonocyclic group containing 1 to 2 oxygen
atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl,
isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-
oxadiazolyl, 1,2,5-oxadiazolyl, etc.), etc.;

saturated 3 to 8-membered (more preferably 5 or 6-
35 membered) heteromonocyclic group containing 1 to 2 oxygen

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atom(s) and 1 to 3 nitrogen atom(s), for example, morpholinyl, sydnonyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolyl, isothiazolyl, thiadiazolyl (e.g., 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.), dihydrothiazinyl, etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiomorpholinyl, thiazolidinyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s), for example, thienyl, dihydrodithiinyl, dihydrodithionyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiazolyl, benzothiadiazolyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom, for example, furyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s), for example, dihydrooxathiinyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s), for example, benzothienyl, benzodithiinyl, etc.;

unsaturated condensed heterocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s), for example, benzoxathiinyl, etc.; and the like.

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The acyl moiety as stated above may have one to ten, same or different, suitable substituent(s).

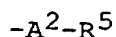
The preferred embodiments of R¹, R² and R³ are as follows.

R¹ is cyano, thiocarbamoyl,
a group of the formula :



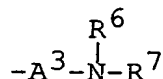
wherein R⁴ is hydrogen, lower alkyl, phenyl(lower)alkyl, di(lower alkoxy)phenyl(lower)alkyl, phenyl(lower)alkoxycarbonyl, phenyl, lower alkoxyphenyl, lower alkylthio or 1-lower alkylindolyl,

A¹ is lower alkylene, and
m and n are each 0 or 1,
a group of the formula :



wherein R⁵ is morpholino, piperidino, 4-phenylpiperazin-1-yl, phthalimido, 1,2,3,4-tetrahydroquinolin-1-yl, 1,2,3,4-tetrahydroisoquinolin-2-yl or imidazol-1-yl, and

A² is lower alkylene, or
a group of the formula :



wherein R⁶ and R⁷ are each hydrogen, phenyl, lower alkanoyl, phenyl(lower)alkoxycarbonyl,

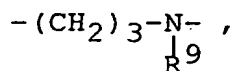
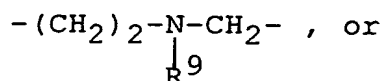
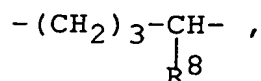
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pyridyl(lower)alkyl, thienyl(lower)alkyl,
 3,4-dihydroisoquinoliny, (lower
 alkylimino)(phenyl)methyl, lower alkyl,
 phenyl(lower)alkyl, naphthyl(lower)alkyl,
 5 (mono- or di- or trilower alkyl)phenyl-
 (lower)alkyl, (mono- or di- or trilower
 alkoxy)phenyl(lower)alkyl, (mono- or di-
 or trihalo)phenyl(lower)alkyl,
 [trihalo(lower)alkoxy]phenyl(lower)alkyl
 10 or [lower alkoxy][trihalo(lower)alkoxy]-
 phenyl(lower)alkyl, and

A^3 is lower alkylene, and

R^2 is hydrogen; or

R^1 and R^2 are linked together to form



wherein R^8 is amino or lower alkanoylamino, and

R^9 is hydrogen, phenyl(lower)alkoxycarbonyl or
 phenyl(lower)alkyl, and

R^3 is 1-lower alkylindolyl, benzofuranyl,
 30 dihydrobenzofuranyl, or
 N,N-di(lower alkyl)aminophenyl.

Further, the preferred embodiments of R^1 , R^2 and R^3 are
 35 as follows.

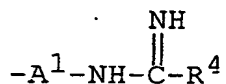
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R¹ is cyano, thiocarbamoyl,
a group of the formula :

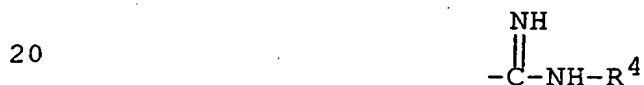


wherein R⁴ is hydrogen or phenyl(lower)alkoxycarbonyl,
and

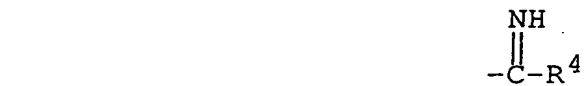
10 A¹ is lower alkylene,
a group of the formula :



15 wherein R⁴ is phenyl or 1-lower alkylindolyl, and
A¹ is lower alkylene,
a group of the formula :



25 wherein R⁴ is hydrogen, lower alkyl, phenyl(lower)alkyl,
di(lower alkoxy)phenyl(lower)alkyl,
phenyl or lower alkoxyphenyl,
a group of the formula :



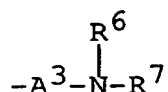
wherein R⁴ is lower alkylthio,
a group of the formula :



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wherein R⁵ is morpholino, piperidino, 4-phenylpiperazin-1-yl, phthalimido, 1,2,3,4-tetrahydroquinolin-1-yl, 1,2,3,4-tetrahydroisoquinolin-2-yl or imidazol-1-yl, and

A² is lower alkylene, or
a group of the formula :



wherein R⁶ and R⁷ are each hydrogen, phenyl, lower alkanoyl, phenyl(lower)alkoxycarbonyl, pyridyl(lower)alkyl, thienyl(lower)alkyl, 3,4-dihydroisoquinolinyl, (lower alkylimino)(phenyl)methyl, lower alkyl, phenyl(lower)alkyl, naphthyl(lower)alkyl, (mono- or di- or trilower alkyl)phenyl(lower)alkyl, (mono- or di- or trilower alkoxy)phenyl(lower)alkyl, (mono- or di- or trihalo)phenyl(lower)alkyl, [trihalo(lower)alkoxy]phenyl(lower)alkyl or [lower alkoxy][trihalo(lower)alkoxy]phenyl(lower)alkyl, and

A³ is lower alkylene,

R² is hydrogen and

R³ is 1-lower alkylindolyl, benzofuranyl, dihydrobenzofuranyl or N,N-di(lower alkyl)aminophenyl.

The processes 1 to 4 for preparing the object compounds (I) of the present invention are explained in detail in the following.

Process 1 :

The object compound (I) or a salt thereof can be

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prepared by reacting the compound (II) or a salt thereof with 1,1'-carbonyldiimidazole and continuously by reacting the obtained compound (III) or a salt thereof with the compound (IV) or a salt thereof.

5 The present reaction is usually carried out in a solvent such as dioxane, dimethylsulfoxide, dimethylformamide, diethylformamide, dimethylacetamide, benzene, hexane, tetrahydrofuran, or any other solvent which does not adversely affect the reaction.

10 The reaction temperature is not critical and the reaction is usually carried out under cooling, at ambient temperature or under heating.

Process 2 :

15 The object compound (I) or a salt thereof can be prepared by reacting the compound (IV) or a salt thereof with 1,1'-carbonyldiimidazole and continuously by reacting the obtained compound (V) or a salt thereof with the compound (II) or a salt thereof.

20 The reaction can be carried out in a similar manner to that of the aforementioned Process 1.

Process 3 :

25 The object compound (I) or a salt thereof can be prepared by subjecting the compound (VI) or a salt thereof to Curtius Rearrangement reaction and continuously by reacting the obtained compound (VII) or a salt thereof with the compound (IV) or a salt thereof.

30 Curtius Rearrangement reaction may be carried out by using a conventional reagent such as diphenylphosphoryl azide.

 The reaction may be also carried out in the presence of an organic or inorganic base such as an alkali metal bicarbonate, tri(lower)alkylamine, pyridine, N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, or
35 the like.

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The reaction temperature is not critical, and the reaction is usually carried out under cooling to heating.

Process 4 :

5 The object compound (I) or a salt thereof can be prepared by subjecting the compound (VIII) or a salt thereof to Curtius Rearrangement reaction and continuously by reacting the obtained compound (IX) or a salt thereof with the compound (II) or a salt thereof.

10 This reaction can be carried out in a similar manner to that of the aforementioned Process 3.

15 The object compound (I) of the present invention can be isolated and purified in a conventional manner, for example, extraction, precipitation, fractional crystallization, recrystallization, chromatography, and the like.

 The object compound (I) thus obtained can be converted to its salt by a conventional method.

20 The object compound (I) and a pharmaceutically acceptable salt thereof may include a solvate [e.g., enclosure compound (e.g., hydrate, etc.)].

25 The object compound (I) of the present invention are novel and exhibit pharmacological activities such as 5-HT antagonism, especially, 5-HT_{2C} antagonism, and the like and therefore are useful as 5-HT antagonist for treating or preventing central nervous system (CNS) disorders such as anxiety, depression, obsessive compulsive disorders, migraine, anorexia, Alzheimer's disease, sleep disorders, bulimia, panic attacks, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines,
30 schizophrenia, and also disorders associated with spinal trauma and/or head injury such as hydrocephalus, and the like.

35 In order to illustrate the usefulness of the object

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compounds (I), pharmacological activity of representative compound of the present invention are shown below.

Test Method :

5

[³H]-mesulergine binding

The affinity of test drugs for the 5-HT_{2C} binding site can be determined by assessing their ability to displace [³H]-mesulergine in the rat prefrontal cortex. The method employed was similar to that of Pazos et al, 1984.

The membrane suspension (500 µl) was incubated with [³H]-mesulergine (1 nM) in Tris HCl buffer containing CaCl₂ 4 mM and ascorbic acid 0.1% (pH 7.4) at 37°C for 30 minutes. Non-specific binding was measured in the presence of mianserin (1 µM). 30 nM spiperone was used to prevent binding to 5-HT_{2A} sites. Test drugs (10⁻⁶ M) were added in a volume of 100 µl. The total assay volume was 1000 µl. Incubation was stopped by rapid filtration using a Brandel cell harvester and radioactivity measured by scintillation counting.

The IC₅₀ values were determined using a four parameter logistic program (DeLean 1978) and the pKi (the negative logarithm of the inhibition constant) calculated from the Cheng Prusoff equation where :

30

$$K_i = \frac{IC_{50}}{1 + C/K_d}$$

K_i = inhibition constant

C = concentration of [³H]-mesulergine

K_d = affinity of mesulergine for 5-HT_{2C} binding sites.

35

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Test Compounds :

(1) N-(1-Methyl-1H-indol-5-yl)-N'-(3-pyridyl)urea
(Reference compound (A))

(2) N-[3-(Butylamidino)phenyl]-N'-[1-methyl-1H-indol-5-yl]urea hydroiodide

(3) N-[3-(Benzylamidino)phenyl]-N'-[1-methyl-1H-indol-5-yl]urea hydroiodide

(4) N-[3-[2-(3,4-Dimethoxyphenyl)ethyl]amidinophenyl]-N'-[1-methyl-1H-indol-5-yl]urea hydroiodide

15 Test Result :

Compound	Inhibition (%)
(1)	21
(2)	77
(3)	83
(4)	82

For therapeutic or preventive administration, the object compound (I) of the present invention are used in the form of conventional pharmaceutical preparation which contains said compound as an active ingredient, in admixture with pharmaceutically acceptable carriers such as an organic or inorganic solid or liquid excipient which is suitable for oral, parenteral and external administration. The pharmaceutical preparations may be in solid form such as tablet, granule, powder, capsule, or liquid form such as solution, suspension, syrup, emulsion, lemonade and the like.

If needed, there may be included in the above preparations auxiliary substances, stabilizing agents,

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wetting agents and other commonly used additives such as lactose, citric acid, tartaric acid, stearic acid, magnesium stearate, terra alba, sucrose, corn starch, talc, gelatin, agar, pectin, peanut oil, olive oil, cacao butter, ethylene glycol, and the like.

While the dosage of the compound (I) may vary from and also depend upon the age, conditions of the patient, a kind of diseases or conditions, a kind of the compound (I) to be applied, etc. In general amounts between 0.01 mg and about 500 mg or even more per day may be administered to a patient. An average single dose of about 0.05 mg, 0.1 mg, 0.25 mg, 0.5 mg, 1 mg, 20 mg, 50 mg, 100 mg of the object compound (I) of the present invention may be used in treating diseases.

The following Preparations and Examples are given for the purpose of illustrating the present invention.

Preparation 1

A mixture of 3-nitrobenzyl bromide (1 g) and 4-methoxybenzylamine (2.26 g) in chloroform (20 ml) was refluxed for 3 hours. This solution was washed with 1N aqueous sodium hydroxide solution twice, dried over magnesium sulfate, filtered, and evaporated. The residue was chromatographed on silica gel (hexene:chloroform = 1:1) to give N-(4-methoxybenzyl)-3-nitrobenzylamine.

IR (Film) : 3300, 1600, 1580 cm^{-1}

NMR (DMSO- d_6 , δ) : 2.80 (1H, s), 3.62 (2H, s), 3.79 (3H, s), 3.87 (2H, s), 6.85-6.88 (2H, m), 7.23-7.27 (2H, m), 7.60 (1H, t, $J=7.9\text{Hz}$), 7.78 (1H, d, $J=7.6\text{Hz}$), 8.09 (1H, d, $J=8.1\text{Hz}$), 8.38 (1H, s)

Preparation 2

A mixture of 3-nitrobenzyl chloride (1.01 g), diphenylamine (500 mg), potassium hydroxide (993 mg), potassium carbonate (652 mg) and tetra-n-butylammonium

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sulfate (79 mg) in toluene (30 ml) was stirred at 72°C for 3 hours. The mixture was washed with water, dried over magnesium sulfate, filtered, and evaporated. This oil was chromatographed on silica gel (hexane:ethyl acetate = 8:1) to give N-(3-nitrobenzyl)diphenylamine.

IR (Nujol) : 1580, 1520 cm^{-1}

NMR (DMSO- d_6 , δ) : 5.16 (2H, s), 6.90-7.31 (12H, m),
7.62 (1H, t, $J=7.8\text{Hz}$), 7.80 (1H, d, $J=7.7\text{Hz}$), 8.08
(1H, d, $J=8.1\text{Hz}$), 8.19 (1H, s)

10 MASS : 305 (M+1)

Preparation 3

A mixture of N-(4-methoxybenzyl)-3-nitrobenzylamine (1.8 g), benzyloxycarbonyl chloride (1 ml) and triethylamine (1 ml) in toluene (15 ml) was stirred at ambient temperature for 3 hours. This solution was washed with water twice, dried over magnesium sulfate, filtered, and evaporated. The residue was chromatographed on silica gel (chloroform) to give N-(benzyloxycarbonyl)-N-(4-methoxybenzyl)-3-nitrobenzylamine.

IR (Film) : 3450, 1690, 1600 cm^{-1}

NMR (DMSO- d_6 , δ) : 3.72 (3H, s), 4.45 (2H, s), 4.54
(2H, s), 5.16 (2H, s), 6.84-6.88 (2H, m), 7.11-8.11
(11H, m)

25

Preparation 4

The following compound was obtained according to a similar manner to that of Preparation 3.

30 N-(Benzyloxycarbonyl)-N-(4-methylbenzyl)-3-nitrobenzylamine

IR (Film) : 3000, 2900, 1680 cm^{-1}

NMR (DMSO- d_6 , δ) : 2.27 (3H, s), 4.47 (2H, s), 4.54
(2H, s), 5.16 (2H, s), 7.12-7.4 (9H, m), 7.5-7.8
(2H, m), 7.90-8.12 (2H, m)

35

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Preparation 5

A mixture of N-(3-nitrobenzyl)diphenylamine (400 mg), ferric chloride (150 mg), active carbon (700 mg) and hydrazine monohydrate (260 mg) in ethanol (15 ml) was stirred at 70°C for 2 hours. The mixture was filtered, evaporated. The residue was dissolved in chloroform, washed with water, dried over sodium sulfate, filtered, and evaporated to give 3-(N,N-diphenylaminomethyl)aniline.

IR (Nujol) : 1575, 1520 cm^{-1}

NMR (DMSO- d_6 , δ) : 4.83 (2H, s), 5.01 (2H, s), 6.36-6.47 (2H, m), 6.56 (1H, s), 6.86-7.28 (11H, m)

MASS : 275 (M+1)

Example 1

A solution of m-aminobenzonitrile (3.01 g) and 1,1'-carbonyldiimidazole (4.14 g) in tetrahydrofuran (30 ml) was stirred at room temperature for 5 hours. A solution of 5-amino-1-methylindole (2.48 g) in tetrahydrofuran (20 ml) was added to the solution. The solution was stirred at room temperature for 48 hours. After evaporation of the solvent, the residue was dissolved in chloroform-methanol (7:3, V/V). The solution was evaporated in vacuo to the volume of 15 ml. The solution was diluted with methanol and allowed to stand at room temperature overnight. The crystals formed was collected and washed with methanol to give N-(3-cyanophenyl)-N'-(1-methyl-1H-indol-5-yl)urea (2.48 g). From the filtrate, another crop of the product (0.82 g) was obtained in a similar manner to that described above.

mp : 203-208°C

IR (Nujol) : 3280, 2220, 1630, 1555 cm^{-1}

NMR (DMSO- d_6 , δ) : 3.76 (3H, s), 6.35 (1H, d, J=3Hz), 7.14-7.75 (7H, m), 8.00 (1H, s), 8.60 (1H, s), 8.93 (1H, s)

35 Example 2

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To a solution of N-(3-cyanophenyl)-N'-(1-methyl-1H-indol-5-yl)urea (2.99 g) in pyridine (30 ml) and triethylamine (10 ml) was passed through slowly hydrogen sulfide gas for 8 hours at room temperature. After 12 hours the solution was diluted with water and stirred for 2 hours. The precipitate formed was collected and washed with water to give N-(1-methyl-1H-indol-5-yl)-N'-(3-thiocarbamoylphenyl)-urea (3.19 g).

mp : 211-214°C

IR (Nujol) : 3290, 3180, 1625, 1604, 1568 cm⁻¹

NMR (DMSO-d₆, δ) : 3.76 (3H, s), 6.34 (1H, d, J=3Hz), 7.12-7.70 (7H, m), 7.95 (1H, s), 8.42 (1H, s), 8.76 (1H, s), 9.46 (1H, s), 9.84 (1H, s)

15 Example 3

To a solution of N-(1-methyl-1H-indol-5-yl)-N'-(3-thiocarbamoylphenyl)urea (1.87 g) in a mixture of acetonitrile (8 ml) and N,N-dimethylformamide (15 ml) was added methyliodide (2 ml). After 24 hours, the solution was diluted with ether. The precipitate formed was collected and washed with ether to give N-(1-methyl-1H-indol-5-yl)-N'-[3-[methylthio(imino)methyl]phenyl]urea hydroiodide (2.60 g).

mp : 187-196°C

IR (Nujol) : 3270, 3150, 1675, 1590, 1555 cm⁻¹

NMR (DMSO-d₆, δ) : 2.85 (3H, s), 3.77 (3H, s), 6.36 (1H, d, J=3Hz), 7.15-7.70 (8H, m), 8.22 (1H, s), 8.60 (1H, s), 9.03 (1H, s)

Example 4

A mixture of N-(1-methyl-1H-indol-5-yl)-N'-[3-[methylthio(imino)methyl]phenyl]urea (0.51 g) and aniline (0.20 g) in N,N-dimethylformamide (3 ml) was stirred at 70°C for 8 hours. After evaporation of the solvent, the residue was neutralized with 1N aqueous sodium hydroxide solution and extracted twice with butanol. The butanol layer was

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evaporated in vacuo. The residue was purified by column chromatography on silica gel (15% methanol in chloroform) to give N-[1-methyl-1H-indol-5-yl]-N'-[3-(phenylamidino)-phenyl]urea (80 mg) as an amorphous powder.

5 IR (Nujol) : 3430, 3300, 1690, 1630, 1570 cm^{-1}

NMR (DMSO- d_6 , δ) : 3.75 (3H, s), 6.22 (1H, br s), 6.34 (1H, d, $J=3\text{Hz}$), 6.80-7.60 (13H, m), 7.70 (1H, d, $J=2\text{Hz}$), 8.03 (1H, s), 8.42 (1H, s), 8.70 (1H, s)

10 Example 5

A mixture of N-(1-methyl-1H-indol-5-yl)-N'-[3-[methylthio(imino)methyl]phenyl]urea (0.60 g) and ammonium acetate (0.30 g) in methanol (6 ml) was heated at 65°C for 7 hours. After cooling, the precipitate formed was collected and washed with methanol to give N-(3-amidinophenyl)-N'-(1-methyl-1H-indol-5-yl)urea hydroiodide (75 mg).

mp : 214-218°C

IR (Nujol) : 3340, 3260, 1690, 1640, 1560, 1525 cm^{-1}

20 NMR (DMSO- d_6 , δ) : 3.75 (3H, s), 6.32 (1H, d, $J=3\text{Hz}$), 7.20-7.80 (9H, m), 7.97 (1H, s), 9.60-10.40 (4H, m)

Example 6

A mixture of N-(1-methyl-1H-indol-5-yl)-N'-[3-[methylthio(imino)methyl]phenyl]urea (300 mg), butylamine (188 mg), and acetic acid (154 mg) in methanol (3 ml) was stirred at 60°C for 6 hours. After evaporation of the solvent, the residue was washed once with ether and twice with water. The oil was dissolved in methanol and the solution was evaporated in vacuo. The residue was triturated with ether and the powder obtained was collected and washed with ether to give N-[3-(butylamidino)phenyl]-N'-(1-methyl-1H-indol-5-yl)urea hydroiodide (274 mg) as an amorphous powder.

IR (Nujol) : 3250, 1660, 1590, 1540 cm^{-1}

35 NMR (DMSO- d_6 , δ) : 0.93 (3H, t, $J=7\text{Hz}$), 1.39 (2H, m),

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1.61 (2H, m), 3.36 (2H, t, J=7Hz), 3.75 (3H, s),
6.33 (1H, d, J=3Hz), 7.10-6.80 (7H, m), 8.00 (1H,
s), 9.66 (1H, s), 10.10 (1H, s)

5 Example 7

N-[3-(Benzylamidino)phenyl]-N'-[1-methyl-1H-indol-5-yl]urea hydroiodide was prepared in a similar manner to that of Example 6.

IR (Nujol) : 3250, 1660, 1620, 1580, 1540 cm^{-1}

10 NMR (DMSO- d_6 , δ) : 3.76 (3H, s), 4.66 (2H, s), 6.35
(1H, d, J=3Hz), 7.10-7.70 (12H, m), 7.99 (1H, s),
8.59 (1H, s), 8.96 (1H, s), 8.60-9.60 (3H, br s)

Example 8

15 N-[3-[2-(3,4-Dimethoxyphenyl)ethyl]amidinophenyl]-N'-[1-methyl-1H-indol-5-yl]urea hydroiodide was prepared in a similar manner to that of Example 6.

IR (Nujol) : 3250, 1665, 1585, 1560 cm^{-1}

20 NMR (DMSO- d_6 , δ) : 2.90 (2H, br t, J=7Hz), 3.62 (2H,
br t, J=7Hz), 3.72 (3H, s), 3.76 (6H, s), 6.34 (1H, -
d, J=3Hz), 6.70-7.80 (9H, m), 8.00 (1H, s), 9.03
(1H, s), 9.41 (1H, s)

Example 9

25 N-[3-(4-Methoxyphenylamidino)phenyl]-N'-[1-methyl-1H-indol-5-yl]urea hydroiodide was prepared in a similar manner to that of Example 6.

IR (Nujol) : 3250, 1660, 1600, 1550, 1510 cm^{-1}

30 NMR (DMSO- d_6 , δ) : 3.76 (3H, s), 3.82 (3H, s), 6.35
(1H, d, J=3Hz), 7.10-7.75 (12H, m), 8.12 (1H, s),
8.61 (1H, s), 8.97 (1H, s)

Example 10

35 N-(Benzofuran-5-yl)-N'-(3-cyanophenyl)urea was prepared in a similar manner to that of Example 1.

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mp : 180-187°C

IR (Nujol) : 3270, 2230, 1630, 1600, 1560 cm⁻¹NMR (DMSO-d₆, δ) : 6.93 (1H, m), 7.25-8.00 (8H, m),
8.83 (1H, s), 9.00 (1H, s)

5

Example 11

N-(Benzofuran-5-yl)-N'-(3-thiocarbamoylphenyl)urea was prepared in a similar manner to that of Example 2.

mp : 188-194°C

10 IR (Nujol) : 3280, 3170, 1625, 1600, 1565 cm⁻¹NMR (DMSO-d₆, δ) : 6.92 (1H, m), 7.25-8.00 (8H, m),
8.66 (1H, s), 8.84 (1H, s), 9.46 (1H, s), 9.84 (1H, s)

15

Example 12

N-(Benzofuran-5-yl)-N'-[3-[methylthio(imino)methyl]-phenyl]urea hydroiodide was prepared in a similar manner to that of Example 3.

mp : 190-196°C

20 IR (Nujol) : 3180, 1675, 1590, 1550 cm⁻¹NMR (DMSO-d₆, δ) : 2.86 (3H, s), 6.94 (1H, m),
7.30-8.20 (8H, m), 8.84 (1H, s), 9.12 (1H, s)Example 13

25 10% Pd-C (100 mg) was added to a solution of 1-methyl-5-nitroindole (500 mg) in ethanol (20 ml). This mixture was hydrogenated at 1 atm at ambient temperature for 2 hours. The mixture was filtered through celite and evaporated. The resulting oil was coevaporated with toluene. To the
30 resulting mass, 1,1'-carbonyldiimidazole (460 mg) was added. This mixture was stirred at ambient temperature for 4 hours. To this solution, 3-(dimethylaminomethyl)aniline (341 mg) was added. This mixture was stirred at ambient temperature overnight, evaporated, and partitioned between chloroform (50
35 ml) and water (20 ml). The organic layer was washed with

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water (2 x 20 ml), dried with magnesium sulfate, filtered, and evaporated. The residue was chromatographed over silica gel (chloroform) and recrystallized from methanol - ethyl acetate to give N-(3-dimethylaminomethylphenyl)-N'-(1-methylindol-5-yl)urea.

mp : 128-133°C

IR (Nujol) : 1630 cm⁻¹

NMR (DMSO-d₆, δ) : 2.16 (6H, s), 2.96 (1H, d, J=3.0Hz), 3.75 (3H, s), 6.86 (1H, d, J=6.9Hz), 7.12-7.35 (5H, m), 7.45 (1H, s), 7.69 (1H, d, J=1.7Hz), 8.42 (1H, s), 8.59 (1H, s)

Example 14

N-(1-Methylindol-5-yl)-N'-[3-[(4-phenylpiperazin-1-yl)methyl]phenyl]urea was prepared in a similar manner to that of Example 13.

mp : 183-185°C

IR (Nujol) : 1610 cm⁻¹

NMR (DMSO-d₆, δ) : 2.4-2.6 (4H, m), 3.08-3.23 (4H, m), 3.49 (2H, s), 3.75 (3H, s), 6.34 (1H, d, J=3.0Hz), 6.76 (1H, t, J=7.3Hz), 6.89-6.94 (3H, m), 7.11-7.38 (7H, m), 7.47 (1H, s), 7.68 (1H, s), 8.39 (1H, s), 8.59 (1H, s)

Example 15

N-(1-Methylindol-5-yl)-N'-(3-piperidinomethylphenyl)urea was prepared in a similar manner to that of Example 13.

mp : 172-173°C

IR (Nujol) : 1625 cm⁻¹

NMR (DMSO-d₆, δ) : 1.3-1.6 (6H, m), 2.25-2.45 (4H, m), 3.37 (2H, s), 3.75 (3H, s), 6.34 (1H, d, J=3.0Hz), 6.85 (1H, d, J=7.4Hz), 7.11-7.40 (6H, m), 7.68 (1H, d, J=1.8Hz), 8.36 (1H, s), 8.56 (1H, s)

Example 16

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N-(1-Methylindol-5-yl)-N'-(3-morpholinomethylphenyl)urea was prepared in a similar manner to that of Example 13.

mp : 174-175°C

IR (Nujol) : 1650, 1615 cm^{-1}

5 NMR (DMSO- d_6 , δ) : 2.36 (4H, t, $J=4.4\text{Hz}$), 3.42 (2H, s), 3.58 (4H, t, $J=4.4\text{Hz}$), 3.75 (3H, s), 6.34 (1H, d, $J=2.7\text{Hz}$), 6.88 (1H, d, $J=7.4\text{Hz}$), 7.11-7.36 (5H, m), 7.44 (1H, s), 7.69 (1H, d, $J=1.8\text{Hz}$), 8.38 (1H, s), 8.57 (1H, s)

10

Example 17

N-(1-Methylindol-5-yl)-N'-(4-phthalimidomethylphenyl)-urea was prepared in a similar manner to that of Example 13.

IR (Nujol) : 1760, 1700, 1665 cm^{-1}

15 NMR (DMSO- d_6 , δ) : 3.75 (3H, s), 4.41 (2H, s), 6.33 (1H, d, $J=3\text{Hz}$), 7.12 (1H, dd, $J=9\text{Hz}$, 2Hz), 7.20-7.45 (6H, m), 7.67 (1H, d, $J=2\text{Hz}$), 7.80-7.95 (4H, m), 8.40 (1H, s), 8.59 (1H, s)

20

Example 18

N-[3-(1-Formylaminoethyl)phenyl]-N'-(1-methylindol-5-yl)urea was prepared in a similar manner to that of Example 13.

mp : 165-168°C

25 IR (Nujol) : 1650, 1635 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.36 (3H, d, $J=7\text{Hz}$), 3.75 (3H, s), 4.80-5.10 (1H, m), 6.34 (1H, d, $J=3\text{Hz}$), 6.80-6.95 (1H, m), 7.10-7.50 (6H, m), 7.69 (1H, d, $J=2\text{Hz}$), 8.03 (1H, s), 8.40 (1H, s), 8.50-8.60 (2H, m)

30

MASS : 337 ($\text{M}+1^{\oplus}$)

Example 19

N-[3-(N-Methylanilino)methylphenyl]-N'-(1-methylindol-5-yl)urea was prepared in a similar manner to that of Example 13.

35

mp : 143-144°C

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IR (Nujol) : 1610 cm^{-1}

NMR (DMSO- d_6 , δ) : 3.02 (3H, s), 3.75 (3H, s), 4.52
(2H, s), 7.33 (1H, d, $J=3.0\text{Hz}$), 6.60-6.81 (4H, m),
7.09-7.40 (8H, m), 7.67 (1H, d, $J=1.7\text{Hz}$), 8.35 (1H,
s), 8.54 (1H, s)

MASS : 385 (M+1)

Example 20

N-(1-Methylindol-5-yl)-N'-[3-(1,2,3,4-
tetrahydroquinolin-1-yl)methylphenyl]urea was prepared in a
similar manner to that of Example 13.

mp : 181-184°C

IR (Nujol) : 1610 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.19-1.99 (2H, m), 2.74 (2H, t,
 $J=6.1\text{Hz}$), 3.38 (2H, t, $J=5.4\text{Hz}$), 3.75 (3H, s), 4.43
(2H, s), 6.33-6.34 (1H, m), 6.42-6.49 (2H, m),
6.82-6.91 (3H, m), 7.10-7.40 (6H, m), 7.66 (1H, s),
8.33 (1H, s), 8.53 (1H, s)

MASS : 411 (M+1)

Example 21

N-(1-Methylindol-5-yl)-N'-(3-anilinomethylphenyl)urea
was prepared in a similar manner to that of Example 13.

mp : 129-131°C

IR (Nujol) : 1610 cm^{-1}

NMR (DMSO- d_6 , δ) : 3.75 (3H, s), 4.22 (2H, d,
 $J=5.9\text{Hz}$), 6.19 (1H, t, $J=5.8\text{Hz}$), 6.33 (1H, d,
 $J=2.9\text{Hz}$), 6.47-6.59 (2H, m), 6.92-7.40 (9H, m),
7.67 (1H, s), 8.35 (1H, s), 8.52 (1H, s)

MASS : 371 (M+1)

Example 22

N-(1-Methylindol-5-yl)-N'-[3-(1,2,3,4-
tetrahydroisoquinolin-2-yl)methylphenyl]urea was prepared in
a similar manner to that of Example 13.

- 30 -

mp : 189-190°C

IR (Nujol) : 1620, 1540 cm^{-1}

NMR (DMSO- d_6 , δ) : 2.70 (2H, d, $J=5.2\text{Hz}$), 2.81 (2H, d, $J=5.2\text{Hz}$), 3.54 (2H, s), 3.61 (2H, s), 3.75 (3H, s),
5 6.33 (1H, d, $J=3.0\text{Hz}$), 6.91-7.50 (10H, m), 7.68
(1H, s), 7.69 (1H, s), 8.37 (1H, s), 8.56 (1H, s)

MASS : 411 (M+1)

Example 23

10 N-(1-Methylindol-5-yl)-N'-(3-phthalimidomethylphenyl)-
urea was prepared in a similar manner to that of Example 13.

mp : 222-226°C

IR (Nujol) : 1700, 1610 cm^{-1}

15 NMR (DMSO- d_6 , δ) : 3.75 (3H, s), 4.74 (2H, s), 6.33
(1H, d, $J=3.0\text{Hz}$), 6.87-7.44 (8H, m), 7.84-7.95 (4H,
m), 8.56 (1H, s), 8.80 (1H, s)

MASS : 425 (M+1)

Example 24

20 N-(1-Methylindol-5-yl)-N'-(3-diphenylaminomethylphenyl)-
urea was prepared in a similar manner to that of Example 13.

mp : 194-195°C

IR (Nujol) : 1610 cm^{-1}

25 NMR (DMSO- d_6 , δ) : 3.75 (3H, s), 4.97 (2H, s), 6.33
(1H, d, $J=3.0\text{Hz}$), 6.88-7.40 (17H, m), 7.66 (1H, d,
 $J=1.8\text{Hz}$), 8.35 (1H, s), 8.57 (1H, s)

MASS : 447 (M+1)

Example 25

30 N-[3-(1-Anilinoethyl)phenyl]-N'-(1-methylindol-5-yl)urea
was prepared in a similar manner to that of Example 13.

mp : 158-162°C

IR (Nujol) : 1650, 1600 cm^{-1}

35 NMR (DMSO- d_6 , δ) : 1.42 (3H, d, $J=7\text{Hz}$), 3.75 (3H, s),
4.38 (1H, quint., $J=7\text{Hz}$), 6.14 (1H, d, $J=6\text{Hz}$), 6.33

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(1H, d, J=3Hz), 6.40-6.55 (3H, m), 6.90-7.45 (9H, m), 7.68 (1H, s), 8.36 (1H, s), 8.52 (1H, s)
MASS : 385 (M+1⁺)

Example 26

5 N-[3-(Imidazol-1-ylmethyl)phenyl]-N'-(1-methylindol-5-yl)urea was prepared in a similar manner to that of Example 13.

mp : 170-175°C

IR (Nujol) : 1630 cm⁻¹

10 NMR (DMSO-d₆, δ) : 3.75 (3H, s), 5.17 (2H, s), 6.34 (1H, d, J=3Hz), 6.82 (1H, d, J=8Hz), 6.92 (1H, s), 7.05-7.45 (7H, m), 7.68 (1H, d, J=2Hz), 7.75 (1H, s), 8.40 (1H, s), 8.61 (1H, s)
MASS : 346 (M+1⁺)

15 Example 27

N-(8-Formylamino-5,6,7,8-tetrahydro-2-naphthyl)-N'-(1-methylindol-5-yl)urea was prepared in a similar manner to that of Example 13.

IR (Nujol) : 1630 cm⁻¹

20 NMR (DMSO-d₆, δ) : 1.60-2.00 (4H, m), 2.66 (2H, br s), 3.75 (3H, s), 5.00-5.10 (1H, m), 6.33 (1H, d, J=3Hz), 6.99 (1H, d, J=8Hz), 7.11 (1H, dd, J=9Hz, 2Hz), 7.20-7.40 (4H, m), 7.67 (1H, d, J=2Hz), 8.12 (1H, s), 8.30 (1H, s), 8.40-8.60 (2H, m)

25 Example 28

N-(2-Benzyloxycarbonyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(1-methylindol-5-yl)urea was prepared in a similar manner to that of Example 13.

30 mp : 218-222°C

IR (Nujol) : 1700, 1660, 1615 cm⁻¹

NMR (DMSO-d₆, δ) : 2.73 (2H, br t, J=6Hz), 3.62 (2H, br t, J=6Hz), 3.75 (3H, s), 4.55 (2H, br s), 5.13 (2H, s), 6.33 (1H, d, J=3Hz), 7.03-7.40 (6H, m), 7.68 (1H, d, J=2Hz), 8.43 (1H, br s), 8.49 (1H, br s)

35

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MASS : 455 (M+1[⊕])Example 29

5 N-(2-Benzyloxycarbonyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-N'-(1-methylindol-5-yl)urea was prepared in a similar manner to that of Example 13.

mp : 153-156°C

IR (Nujol) : 1690, 1630 cm⁻¹

10 NMR (DMSO-d₆, δ) : 2.71 (2H, br t, J=6Hz), 3.69 (2H, br t, J=6Hz), 3.75 (3H, s), 4.59 (2H, br s), 5.13 (2H, s), 6.33 (1H, d, J=3Hz), 6.88 (1H, d, J=8Hz), 7.10-7.40 (9H, m), 7.60-7.80 (2H, m), 7.88 (1H, br s), 8.76 (1H, br s)

MASS : 455 (M+1[⊕])Example 30

15 N-(2-Benzyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-N'-(1-methylindol-5-yl)urea was prepared in a similar manner to that of Example 13.

mp : 165-167°C

IR (Nujol) : 1635 cm⁻¹

20 NMR (DMSO-d₆, δ) : 2.55-2.80 (4H, m), 3.50 (2H, s), 3.64 (2H, s), 3.75 (3H, s), 6.32 (1H, d, J=3Hz), 6.90-7.40 (11H, m), 7.66 (1H, s), 8.37 (2H, br s)

MASS : 411 (M+1[⊕])Example 31

25 N-(1-Benzyloxycarbonyl-1,2,3,4-tetrahydroquinolin-7-yl)-N'-(1-methylindol-5-yl)urea was prepared in a similar manner to that of Example 13.

IR (Nujol) : 1680, 1640, 1610 cm⁻¹

30 NMR (DMSO-d₆, δ) : 1.84 (2H, quar., J=6Hz), 2.67 (2H, t, J=6Hz), 3.60-3.76 (5H, m), 5.20 (2H, s), 6.33 (1H, d, J=3Hz), 7.00 (1H, d, J=8Hz), 7.10-7.50 (9H, m), 7.69 (1H, s), 7.84 (1H, s), 8.32 (1H, s), 8.52 (1H, s)

35 Example 32

- 33 -

N-(1-Benzyloxycarbonyl-1,2,3,4-tetrahydroquinolin-5-yl)-N'-(1-methylindol-5-yl)urea was prepared in a similar manner to that of Example 13.

mp : 147-152°C

5 IR (Nujol) : 1700, 1630 cm⁻¹

NMR (DMSO-d₆, δ) : 1.80-2.00 (2H, m), 2.65 (2H, t, J=7Hz), 3.60-3.80 (5H, m), 5.19 (2H, s), 6.33 (1H, d, J=3Hz), 6.90-7.50 (10H, m), 7.60 (1H, d, J=7Hz), 7.71 (1H, d, J=2Hz), 7.84 (1H, s), 8.83 (1H, s)

10

Example 33

N-(2,3-Dihydrobenzo[b]furan-7-yl)-N'-(3-phthalimidomethylphenyl)urea was prepared in a similar manner to that of Example 13.

15 IR (Nujol) : 3260, 1740, 1700, 1640 cm⁻¹

NMR (DMSO-d₆, δ) : 3.21 (2H, t, J=8.6Hz), 4.60 (2H, t, J=8.7Hz), 4.74 (2H, s), 6.71-7.03 (3H, m), 7.19-7.42 (3H, m), 7.66-8.10 (5H, m), 8.67 (1H, s), 9.13 (1H, s)

20 MASS : 414 (M+1)

Example 34

To a solution of N-(benzyloxycarbonyl)-N-(4-methoxybenzyl)-3-nitrobenzylamine (1.5 g) in ethanol (20 ml), were added ferric chloride (50 mg), active carbon (500 mg), and hydrazine monohydrate (2 ml). This mixture was stirred at 70°C for 2 hours, filtered, and evaporated. The residue was dissolved in chloroform and washed with water, dried over magnesium sulfate, filtered, and evaporated. By using this amine, the following compound was obtained according to a similar manner to that of Example 13. N-(1-Methylindol-5-yl)-N'-[3-[N-benzyloxycarbonyl-N-(4-methoxybenzyl)-aminomethyl]phenyl]urea.

30 IR (Nujol) : 3300, 1700, 1610, 1560 cm⁻¹

35 NMR (DMSO-d₆, δ) : 3.74 (3H, s), 3.76 (3H, s), 4.36

- 34 -

(4H, s), 5.18 (2H, s), 6.34 (1H, d, J=2.9Hz), 6.80-6.96 (3H, m), 7.13-7.36 (13H, m), 7.70 (1H, s), 8.41 (1H, s), 8.61 (1H, s)

MASS : 549 (M+1)

5

Example 35

N-(1-Methylindol-5-yl)-N'-[3-[N-benzyloxycarbonyl-N-(4-methylbenzyl)aminomethyl]phenyl]urea was prepared in a similar manner to that of Example 34.

10

IR (Nujol) : 3260, 1690, 1610, 1540 cm^{-1}

NMR (DMSO- d_6 , δ) : 2.29 (3H, s), 3.76 (3H, s), 4.37 (4H, s), 5.18 (2H, s), 6.34 (1H, s, J=2.9Hz), 6.79 (1H, s), 7.13-7.36 (15H, m), 7.70 (1H, s), 8.42 (1H, s), 8.63 (1H, s)

15

Example 36

To a suspension of 1-methylindole-5-carboxylic acid (1.0 g) in benzene were added triethylamine (0.80 ml) and diphenylphosphoryl azide (1.23 ml). The mixture was refluxed for 3 hours. After being cooled, 4-cyanoaniline (1.35 g) was added and refluxed for 7 hours. The reaction mixture was partitioned between water and ethyl acetate. Precipitates were collected, washed with water, and dried to give N-(4-cyanophenyl)-N'-(1-methylindol-5-yl)urea (1.11 g). From the ethyl acetate layer, another 0.41 g of N-(4-cyanophenyl)-N'-(1-methylindol-5-yl)urea was obtained.

25

mp : 238-240°C

IR (Nujol) : 2315, 1695, 1640 cm^{-1}

30

NMR (DMSO- d_6 , δ) : 3.76 (3H, s), 6.36 (1H, d, J=3Hz), 7.15 (1H, dd, J=8Hz, 2Hz), 7.28 (1H, d, J=3Hz), 7.35 (1H, d, J=9Hz), 7.60-7.80 (5H, m), 8.63 (1H, s), 9.11 (1H, s)

MASS : 291(M+1 $^{\oplus}$)

35

Example 37

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N-(3-Cyanophenyl)-N'-(4-dimethylaminophenyl)urea was prepared in a similar manner to that of Example 36.

IR (Nujol) : 3310, 2200, 1640, 1600 cm^{-1}

NMR (DMSO- d_6 , δ) : 2.84 (6H, s), 6.68 (1H, s), 6.73 (1H, s), 7.25 (1H, s), 7.29 (1H, s), 7.37-7.67 (3H, m), 8.32 (1H, s), 8.47 (1H, s), 8.89 (1H, s)

MASS : 281 (M+1)

Example 38

10 N-(3-Cyanophenyl)-N'-(2,3-dihydrobenzo[b]furan-7-yl)urea was prepared in a similar manner to that of Example 36.

IR (Nujol) : 2200, 1650, 1600 cm^{-1}

NMR (DMSO- d_6 , δ) : 3.23 (2H, t, J=8.8Hz), 4.62 (2H, t, J=8.7Hz), 6.74-6.92 (2H, m), 7.40-7.64 (3H, m), 7.80 (1H, d, J=7.3Hz), 7.98 (1H, s), 8.30 (1H, s), 9.41 (1H, s)

MASS : 280 (M+1)

Example 39

20 N-(1-Methylindol-5-yl)-N'-(4-thiocarbamoylphenyl)urea was prepared in a similar manner to that of Example 2.

IR (Nujol) : 1650, 1620, 1590 cm^{-1}

NMR (DMSO- d_6 , δ) : 3.76 (3H, s), 6.35 (1H, d, J=3Hz), 7.15 (1H, dd, J=7Hz, 2Hz), 7.27 (1H, d, J=3Hz), 7.35 (1H, d, J=9Hz), 7.44 (2H, d, J=12Hz), 7.70 (1H, d, J=2Hz), 7.80-8.00 (3H, m), 8.55 (1H, s), 8.91 (1H, s), 9.30 (1H, br s), 9.61 (1H, br s)

Example 40

30 N-(1-Methylindol-5-yl)-N'-[4-[methylthio(imino)methyl]-phenyl]urea hydroiodide was prepared in a similar manner to that of Example 3.

mp : 95-105°C

IR (Nujol) : 1645 cm^{-1}

35 NMR (DMSO- d_6 , δ) : 2.83 (3H, s), 3.77 (3H, s), 6.36

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(1H, d, J=3Hz), 7.17 (1H, dd, J=9Hz, 2Hz), 7.30
(1H, d, J=3Hz), 7.37 (1H, d, J=9Hz), 7.70-7.80 (3H,
m), 7.80-8.10 (2H, m), 8.73 (1H, s), 9.34 (1H, s)
MASS : 339 (M+1)[⊕], 291 (M-48(CH₃SH)+1)[⊕]

5 Example 41

N-(3-Thiocarbamoylphenyl)-N'-(4-dimethylaminophenyl)urea
was prepared in a similar manner to that of Example 2.

IR (Nujol) : 3280, 1620 cm⁻¹

10 NMR (DMSO-d₆, δ) : 2.83 (6H, s), 6.67 (1H, s), 6.72
(1H, s), 7.24-7.39 (4H, m), 7.61-7.66 (1H, m), 7.91
(1H, s), 8.28 (1H, s), 8.71 (1H, s), 9.46 (1H, s),
9.84 (1H, s)

MASS : 315 (M+1)

15 Example 42

N-[3-[Methylthio(imino)methyl]phenyl]-N'-(4-
dimethylaminophenyl)urea hydroiodide was prepared in a
similar manner to that of Example 3.

IR (Nujol) : 1670 cm⁻¹

20 NMR (DMSO-d₆, δ) : 2.86 (3H, s), 3.61 (3H, s), 7.25-
7.76 (5H, m), 7.89 (1H, s), 8.16 (1H, s), 9.25 (1H,
s), 9.29 (1H, s)

MASS : 329 (M+1)

25 Example 43

N-[3-[Methylthio(imino)methyl]phenyl]-N'-(2,3-
dihydrobenzo[b]furan-7-yl)urea hydroiodide was prepared in
similar manners to those of Example 2, and then Example 3.

IR (Nujol) : 1690, 1600 cm⁻¹

30 NMR (DMSO-d₆, δ) : 2.41 (3H, s), 3.23 (2H, t,
J=8.8Hz), 4.62 (2H, t, J=8.7Hz), 6.73-6.90 (2H, m),
7.25-7.51 (3H, m), 7.82-7.86 (1H, s), 8.16-8.20
(1H, m), 9.28 (1H, s), 10.19 (1H, s), 10.36 (1H, s)

MASS : 328 (M+1)

35

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Example 44

N-(4-Amidinophenyl)-N'-(1-methylindol-5-yl)urea
hydroiodide was prepared in a similar manner to that of
Example 5.

5 mp : 167-172°C
IR (Nujol) : 1650, 1630 cm^{-1}
NMR (DMSO- d_6 , δ) : 3.77 (3H, s), 6.35 (1H, d, J=3Hz),
7.17 (1H, dd, J=9Hz, 2Hz), 7.28 (1H, d, J=3Hz),
7.34 (1H, d, J=9Hz), 7.60-7.90 (5H, m), 8.60-9.40
10 (6H, m)
MASS : 308 ($\text{M}+1^{\oplus}$)

Example 45

N-(1-Methylindol-5-yl)-N'-[4-(phenylamidino)phenyl]urea
hydroiodide was prepared in a similar manner to that of
15 Example 6.

mp : >280°C
IR (Nujol) : 1685, 1650 cm^{-1}
NMR (DMSO- d_6 , δ) : 3.77 (3H, s), 6.36 (1H, d, J=3Hz),
7.15 (1H, dd, J=9Hz, 2Hz), 7.29 (1H, d, J=3Hz),
20 7.30-7.65 (6H, m), 7.70-7.75 (3H, m), 7.86 (2H, d,
J=9Hz), 8.66 (1H, s), 9.14 (1H, s)
MASS : 384 ($\text{M}+1^{\oplus}$)

Example 46

N-[4-(Benzylamidino)phenyl]-N'-(1-methylindol-5-yl)urea
25 hydroiodide was prepared in a similar manner to that of
Example 6.

mp : 155-165°C
IR (Nujol) : 1650 cm^{-1}
NMR (DMSO- d_6 , δ) : 3.76 (3H, s), 4.65 (2H, s), 6.35
30 (1H, d, J=3Hz), 7.10-8.10 (16H, m), 9.34 (1H, s),
9.86 (1H, s)
MASS : 398 ($\text{M}+1^{\oplus}$)

Example 47

N-(1-Methylindol-5-yl)-N'-[3-(3-phenylpropyl)-
35 amidinophenyl]urea hydroiodide was prepared in a similar

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manner to that of Example 6.

IR (Nujol) : 3250, 1650, 1580 cm^{-1}

NMR (DMSO- d_6 , δ): 1.70-2.00 (4H, m), 2.70 (2H, m), 3.40 (2H, t, $J=7\text{Hz}$), 3.75 (3H, s), 6.32 (1H, d, $J=3\text{Hz}$), 7.15-7.40 (11H, m), 7.47 (1H, t, $J=9\text{Hz}$), 7.75 (2H, m), 8.06 (1H, s), 9.94 (1H, s), 10.40 (1H, s)

MASS : 426 (M^++1)

Example 48

10 N-(1-Methylindol-5-yl)-N'-[3-(2-phenylethyl)-amidinophenyl]urea hydroiodide was prepared in a similar manner to that of Example 6.

IR (Nujol) : 3250, 1655, 1580, 1540 cm^{-1}

15 NMR (DMSO- d_6 , δ) : 2.97 (2H, t, $J=8\text{Hz}$), 3.36 (2H, t, $J=8\text{Hz}$), 3.76 (3H, s), 6.35 (1H, d, $J=3\text{Hz}$), 7.10-7.40 (12H, m), 7.48 (1H, t, $J=8\text{Hz}$), 7.64 (1H, d, $J=9\text{Hz}$), 7.77 (1H, s), 7.85 (1H, s), 8.92 (1H, s), 9.28 (1H, s)

MASS : 412 (M^++1)

Example 49

20 N-(Benzo[b]furan-5-yl)-N'-[3-(phenylamidino)phenyl]urea hydroiodide was prepared in a similar manner to that of Example 6.

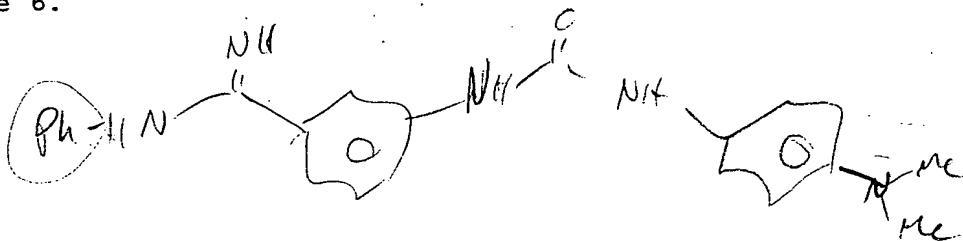
25 IR (Nujol) : 3500-3000, 1650, 1590, 1540 cm^{-1}

NMR (DMSO- d_6 , δ) : 6.60 (1H, m), 6.90-7.00 (1H, m), 7.20-7.60 (10H, m), 7.70 (1H, m), 7.85 (1H, d, $J=2\text{Hz}$), 7.95 (1H, d, $J=2\text{Hz}$), 8.13 (1H, m), 8.83 (1H, s), 9.04 (1H, s)

30 MASS : 371 (M^++1)

Example 50

35 N-[3-(Phenylamidino)phenyl]-N'-(4-dimethylaminophenyl)-urea hydroiodide was prepared in a similar manner to that of Example 6.



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mp : 166-172°C

IR (Nujol) : 1650 cm⁻¹

NMR (DMSO-d₆, δ) : 3.59 (6H, s), 7.36-7.77 (10H, m),
7.88-7.92 (2H, m), 8.10 (1H, s), 9.06 (1H, s),
9.22-9.24 (2H, m), 9.85 (1H, s), 11.43 (1H, s)

MASS : 374 (M+1)

Example 51

N-[3-(Phenylamidino)phenyl]-N'-(2,3-dihydrobenzo[b]-
furan-7-yl)urea hydroiodide was prepared in a similar manner
to that of Example 6.

mp : 97-105°C

IR (Nujol) : 1660 cm⁻¹

NMR (DMSO-d₆, δ) : 3.23 (2H, t, J=8.6Hz), 4.61 (2H, t,
J=8.6Hz), 6.73-7.06 (5H, m), 7.30-7.62 (5H, m),
7.85 (1H, d, J=7.8Hz), 7.99 (1H, s), 8.21 (1H, s),
9.28 (1H, s)

MASS : 373 (M+1)

Example 52

A mixture of N-(1-methylindol-5-yl)-N'-(3-
phthalimidomethylphenyl)urea (420 mg) and hydrazine
monohydrate (150 mg) in ethanol (100 ml) was stirred at 70°C
for 5 hours. After evaporation of the solvent, the residue
was partitioned between ethyl acetate and 1N aqueous sodium
hydroxide. The organic layer was washed with water, dried
over magnesium sulfate, filtered, and evaporated. This
residue was recrystallized from chloroform-hexane to give
N-(1-methylindol-5-yl)-N'-(3-aminomethylphenyl)urea.

mp : 123-126°C

IR (Nujol) : 1610 cm⁻¹

NMR (DMSO-d₆, δ) : 1.81 (2H, s), 3.75 (3H, s), 6.32
(1H, d, J=2.9Hz), 6.90 (1H, d, J=7.5Hz), 7.14-7.48
(8H, m), 7.74 (1H, s), 9.39 (1H, s), 9.51 (1H, s)

MASS : 295 (M+1)

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Example 53

N-(4-Aminomethylphenyl)-N'-(1-methylindol-5-yl)urea was prepared in a similar manner to that of Example 52.

mp : 173-175°C

5 IR (Nujol) : 1635 cm⁻¹

NMR (DMSO-d₆, δ) : 3.65 (2H, s), 3.75 (3H, s), 6.33 (1H, d, J=3Hz), 7.10-7.45 (7H, m), 7.68 (1H, d, J=2Hz), 8.44 (1H, s), 8.54 (1H, s)

MASS (FAB) : 295 (M+1⁺)

10 Example 54

N-(2,3-Dihydrobenzo[b]furan-7-yl)-N'-(3-aminomethylphenyl)urea was prepared in a similar manner to that of Example 52.

mp : 151-153°C

15 IR (Nujol) : 3240, 1650, 1590 cm⁻¹

NMR (DMSO-d₆, δ) : 3.22 (2H, t, J=8.6Hz), 4.02 (2H, s), 4.61 (2H, t, J=8.7Hz), 6.72-6.95 (3H, m), 7.16-7.37 (3H, m), 7.86 (1H, d, J=7.1Hz), 8.17 (1H, s), 9.07 (1H, s)

20 MASS : 284 (M+1)

Example 55

To a solution of 7-nitrobenzo[b]furan (1.23 g) in ethanol (100 ml) were added hydrazine hydrate (660 μl), ferric chloride (20 mg) and active carbon (200 mg). The mixture was stirred at 70°C for 2 hours, filtered, and evaporated. The residue was dissolved in ethyl acetate, and washed with water. The organic layer was dried over magnesium sulfate, filtered, and evaporated to give 7-aminobenzo[b]furan. By using this, the following compound was obtained according to similar manners to those of Example 13, and then Example 52.

N-(3-Aminomethylphenyl)-N'-(benzo[b]furan-7-yl)urea

IR (Nujol) : 1680 cm⁻¹

35 NMR (DMSO-d₆, δ) : 3.71 (2H, s), 6.95-6.98 (2H, m),

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7.13-7.43 (5H, m), 7.98-8.06 (2H, m), 8.87 (1H, s),
9.15 (1H, s)

MASS : 282 (M+1)

5 Example 56

To a mixture of N-(1-methylindol-5-yl)-N'-[3-[(3-benzyloxycarbonylguanidino)methyl]phenyl]urea (100 mg), tetrahydrofuran (10 ml) and methanol (10 ml), 10% palladium on carbon (30 mg) was added. This mixture was hydrogenated
10 at 1 atm at ambient temperature for 1 hour. The mixture was filtered through celite and evaporated. The resulting oil was triturated with diisopropyl ether to give N-(1-methylindol-5-yl)-N'-[3-(guanidinomethyl)phenyl]urea.

IR (Nujol) : 1650, 1540 cm^{-1}

15 NMR (DMSO- d_6 , δ) : 3.75 (3H, s), 4.33 (2H, s), 6.33
 (1H, d, J=2.9Hz), 6.86 (1H, d, J=7.4Hz), 7.14-7.73
 (9H, m)

MASS : 337 (M+1)

20 Example 57

To a mixture of N-(1-methylindol-5-yl)-N'-[3-[N-benzyloxycarbonyl-N-(4-methoxybenzyl)aminomethyl]phenyl]urea (1 g) in methanol (15 ml) and tetrahydrofuran (15 ml) were added 10% palladium on carbon. This mixture was hydrogenated
25 at 1 atm at ambient temperature for 1 hour, filtered and evaporated. The resulting oil was triturated with diisopropyl ether to give N-(1-methylindol-5-yl)-N'-[3-[(4-methoxybenzyl)aminomethyl]phenyl]urea.

mp : 78-80°C

30 IR (Nujol) : 1610, 1540 cm^{-1}

NMR (DMSO- d_6 , δ) : 2.80-3.00 (1H, m), 3.63 (4H, s),
 3.73 (3H, s), 3.75 (3H, s), 6.34 (1H, s), 6.86-6.90
 (3H, m), 7.10-7.50 (6H, m), 7.69 (1H, s), 8.41 (1H,
 s), 8.55 (1H, s)

35 MASS : 415 (M+1)

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Example 58

N-(1-Methylindol-5-yl)-N'-[3-[(4-methylbenzyl)-aminomethyl]phenyl]urea was prepared in a similar manner to that of Example 57.

5 mp : 92-94°C

IR (Nujol) : 1610, 1540 cm⁻¹

NMR (DMSO-d₆, δ) : 2.28 (3H, s), 3.64-3.65 (4H, m),
3.75 (3H, s), 6.34 (1H, d, J=2.9Hz), 6.91 (1H, d,
J=6.9Hz), 7.10-7.43 (11H, m), 7.69 (1H, d,
10 J=1.5Hz), 8.41 (1H, s), 8.56 (1H, s)

MASS : 533 (M+1)

Example 59

15 N-(1-Methylindol-5-yl)-N'-[3-(methylaminomethyl)-phenyl]urea maleate was prepared in similar manners to those of Example 34, and then Example 57.

mp : 172-175°C

IR (Nujol) : 3300, 1630, 1610 cm⁻¹

20 NMR (DMSO-d₆, δ) : 2.56 (3H, s), 3.76 (3H, s), 4.10 (2H, s), 6.04 (2H, s), 6.34 (1H, d, J=2.6Hz), 7.05 (1H, d, J=6.7Hz), 7.15 (1H, dd, J=8.7Hz, 1.9Hz), 7.27-7.42 (4H, m), 7.70-7.71 (2H, m), 8.57 (1H, s), 8.6-8.9 (3H, m)

MASS : 309 (M+1)

25

Example 60

N-(1-Methylindol-5-yl)-N'-(1,2,3,4-tetrahydroisoquinolin-7-yl)urea was prepared in a similar manner to that of Example 57.

30 mp : 174-177°C

IR (Nujol) : 1600, 1640 cm⁻¹

NMR (DMSO-d₆, δ) : 2.63 (2H, t, J=6Hz), 2.96 (2H, t, J=6Hz), 3.75 (3H, s), 3.84 (2H, s), 6.33 (1H, d, J=3Hz), 6.95 (1H, d, J=8Hz), 7.10-7.40 (5H, m),
35 7.68 (1H, d, J=2Hz), 8.45 (1H, s), 8.48 (1H, s)

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MASS : 321 (M+1[⊕])Example 61

5 N-(1-Methylindol-5-yl)-N'-(1,2,3,4-tetrahydroisoquinolin-5-yl)urea was prepared in a similar manner to that of Example 57.

mp : 167-169°C

IR (Nujol) : 1625 cm⁻¹

10 NMR (DMSO-d₆, δ) : 2.55 (2H, t, J=6Hz), 3.03 (2H, t, J=6Hz), 3.76 (3H, s), 3.84 (2H, s), 6.34 (1H, d, J=3Hz), 6.70 (1H, d, J=7Hz), 7.00-7.20 (2H, m), 7.26 (1H, d, J=3Hz), 7.34 (1H, d, J=9Hz), 7.70-7.80 (3H, m), 8.86 (1H, s)
MASS : 321 (M+1[⊕])

Example 62

15 N-(1-Methylindol-5-yl)-N'-(1,2,3,4-tetrahydroquinolin-5-yl)urea was prepared in a similar manner to that of Example 57.

mp : 180-185°C

IR (Nujol) : 1620, 1600 cm⁻¹

20 NMR (DMSO-d₆, δ) : 1.83 (2H, br s), 2.51 (2H, br s), 3.12 (2H, br s), 3.75 (3H, s), 5.59 (1H, br s), 6.17 (1H, d, J=8Hz), 6.33 (1H, d, J=3Hz), 6.70-7.40 (5H, m), 7.57 (1H, s), 7.69 (1H, s), 8.70 (1H, s)
MASS : 321 (M+1[⊕])

25 Example 63

N-(1-Methylindol-5-yl)-N'-(1,2,3,4-tetrahydroquinolin-7-yl)urea was prepared in a similar manner to that of Example 57.

mp : 225-230°C

30 IR (Nujol) : 1640, 1620 cm⁻¹

NMR (DMSO-d₆, δ) : 1.60-1.90 (2H, m), 2.40-2.65 (2H, m), 3.10-3.20 (2H, m), 3.75 (3H, s), 5.60 (1H, br s), 6.32 (1H, d, J=3Hz), 6.45 (1H, dd, J=8Hz, 2Hz), 6.60-6.75 (2H, m), 7.11 (1H, dd, J=9Hz, 2Hz), 7.25 (1H, d, J=3Hz), 7.31 (1H, d, J=9Hz), 7.66 (1H, d,

35

J=2Hz), 8.16 (1H, s), 8.26 (1H, s)
MASS : 321 (M+1[⊕])

Example 64

To a solution of N-[3-(1-formylaminoethyl)phenyl]-N'-(1-methylindol-5-yl)urea (0.30 g) in ethanol (10 ml) was added 1N-aqueous sodium hydroxide (2.7 ml). The mixture was refluxed for 9 hours. After evaporation, resulting mass was partitioned between water and ethyl acetate. Organic layer was dried over sodium sulfate, and chromatographed on silica gel eluted by chloroform-methanol-aqueous ammonia (10:1:0 to 10:1:0.05) to give N-[3-(1-aminoethyl)phenyl]-N'-(1-methylindol-5-yl)urea (0.19 g).

mp : 90-110°C (amorphous)

IR (Nujol) : 1650 cm⁻¹

NMR (DMSO-d₆, δ) : 1.29 (3H, d, J=6Hz), 3.75 (3H, s), 4.03 (1H, q, J=6Hz), 6.33 (1H, d, J=3Hz), 7.10-7.40 (5H, m), 7.47 (1H, s), 7.70 (1H, s), 8.56 (1H, s), 8.70 (1H, s)

MASS : 309 (M+1[⊕]), 617 (2M+1[⊕])

Example 65

N-(8-Amino-5,6,7,8-tetrahydro-2-naphthyl)-N'-(1-methylindol-5-yl)urea was prepared in a similar manner to that of Example 64.

mp : 175-180°C

IR (Nujol) : 1665, 1595 cm⁻¹

NMR (DMSO-d₆, δ) : 1.50-2.10 (4H, m), 2.45-2.70 (2H, m), 3.75 (3H, s), 4.00 (1H, br s), 6.32 (1H, d, J=3Hz), 6.98 (1H, d, J=8Hz), 7.14 (1H, dd, J=9Hz, 2Hz), 7.20-7.35 (3H, m), 7.52 (1H, d, J=2Hz), 7.70 (1H, d, J=2Hz), 8.69 (2H, s)

MASS : 318 (M-NH₂)[⊕]

Example 66

To a solution of N-[4-(aminomethyl)phenyl]-N'-(1-methylindol-5-yl)urea (0.10 g) in N,N-dimethylformamide (5 ml) was added [(methylthio)(imino)methyl]benzene hydroiodide

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(95 mg). The mixture was stirred at 100°C for 5 hours. After being cooled, the mixture was poured into water, alkalized by aqueous sodium hydroxide to pH=12, and extracted with ethyl acetate. The extract was dried over sodium sulfate, evaporated, and chromatographed on silica gel eluted by chloroform-methanol-aqueous ammonia (9:1:0.1, V/V), to give N-[4-[[(imino) (phenyl)methyl]aminomethyl]phenyl]-N'-(1-methylindol-5-yl)urea (0.08 g).

mp : 120-130°C

10 IR (Nujol) : 1650, 1590 cm^{-1}

NMR (DMSO- d_6 , δ) : 3.75 (3H, s), 4.36 (2H, s), 6.33 (1H, d, J=3Hz), 7.14 (1H, dd, J=9Hz, 2Hz), 7.20-7.50 (10H, m), 7.69 (1H, d, J=2Hz), 7.75-7.85 (2H, m), 8.53 (1H, br s), 8.67 (1H, br s)

15 MASS : 398 (M+1⁺)

Example 67

N-(1-Methylindol-5-yl)-N'-[3-[[(imino) (phenyl)methyl]aminomethyl]phenyl]urea hydroiodide was prepared in a similar manner to that of Example 66.

20 mp : 144-147°C

IR (Nujol) : 1650 cm^{-1}

NMR (DMSO- d_6 , δ) : 3.76 (3H, s), 4.67 (2H, s), 6.34 (1H, d, J=2.9Hz), 7.01 (1H, d, J=6.8Hz), 7.15 (1H, dd, J=8.7Hz, 1.9Hz), 7.2-7.4 (5H, m), 7.6-7.9 (9H, m), 8.55 (1H, s), 8.76 (1H, s), 9.1-9.7 (1H, m), 10-10.4 (1H, m)

25 MASS : 398 (M+1)

Example 68

30 N-[3-[1-[[(Imino) (phenyl)methyl]amino]ethyl]phenyl]-N'-[1-methylindol-5-yl]urea was prepared in a similar manner to that of Example 66.

mp : 110-125°C

IR (Nujol) : 1650, 1590 cm^{-1}

35 NMR (DMSO- d_6 , δ) : 1.40 (3H, d, J=7Hz), 3.75 (3H, s),

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4.70-4.80 (1H, m), 6.33 (1H, d, J=3Hz), 6.90 (2H, br s), 7.00-7.50 (10H, m), 7.69 (1H, d, J=2Hz), 7.75-7.85 (2H, m), 8.44 (1H, s), 8.61 (1H, s)
MASS : 412 (M+1[⊕])

5 Example 69

N-(1-Methylindol-5-yl)-N'-[3-[(1-methylindol-5-yl)(imino)methyl]aminomethyl]phenyl]urea hydroiodide was prepared in a similar manner to that of Example 66.

mp : 164-172°C

10 IR (Nujol) : 1640, 1580 cm⁻¹

NMR (DMSO-d₆, δ) : 3.76 (3H, s), 3.88 (3H, s), 4.69 (2H, s), 6.34 (1H, d, J=2.9Hz), 6.67 (1H, d, J=3.1Hz), 7.02 (1H, d, J=6.5Hz), 7.15 (1H, dd, J=8.8Hz, 1.9Hz), 7.27-7.36 (4H, m), 7.56-7.72 (5H, m), 8.15 (1H, s), 8.51 (1H, s), 8.73 (1H, s), 9.00 (1H, s), 9.41 (1H, s), 10.08 (1H, s)

15 MASS : 451 (M+1)

Example 70

20 N-[3-[(Imino)(phenyl)methyl]aminomethyl]phenyl]-N'-(benzo[b]furan-7-yl)urea hydrochloride was prepared in a similar manner to that of Example 66.

mp : 132-165°C

IR (Nujol) : 1680, 1600 cm⁻¹

25 NMR (DMSO-d₆, δ) : 4.71 (2H, d, J=5.9Hz), 6.98-7.48 (6H, m), 7.60-8.05 (8H, m), 9.12 (1H, s), 9.36 (1H, s), 9.66 (1H, s), 9.80 (1H, s), 10.39 (1H, s)

MASS : 385 (M+1)

30 Example 71

N-[3-[(Imino)(phenyl)methyl]aminomethyl]phenyl]-N'-(2,3-dihydrobenzo[b]furan-7-yl)urea hydrochloride was prepared in a similar manner to that of Example 66.

mp : 132-165°C

35 IR (Nujol) : 1660, 1590 cm⁻¹

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NMR (DMSO- d_6 , δ) : 3.22 (2H, t, $J=8.7\text{Hz}$), 4.59 (2H, t, $J=8.7\text{Hz}$), 4.71 (2H, s), 6.72-6.89 (2H, m), 7.03 (1H, d, $J=7.4\text{Hz}$), 7.27-7.43 (2H, m), 7.59-7.86 (7H, m), 8.33 (1H, d, $J=6.3\text{Hz}$), 9.39 (1H, s), 9.58 (1H, s), 9.67 (1H, s), 10.40 (1H, s)

MASS : 387 (M+1)

Example 72

A mixture of N-(1-methylindol-5-yl)-N'-[3-(aminomethyl)phenyl]urea (280 mg) and N-benzyloxycarbonyl-S-methylisothiurea (230 mg) in isopropyl alcohol (15 ml) was heated at 80°C overnight. After evaporation of the solvent, the residue was dissolved in chloroform, washed with 1N aqueous sodium hydroxide solution twice, dried over magnesium sulfate, filtered, and evaporated. The residue was chromatographed on silica gel (2% methanol in chloroform) to give N-(1-methylindol-5-yl)-N'-[3-[(3-benzyloxycarbonyl-guanidino)methyl]phenyl]urea.

IR (Nujol) : 3410, 1650, 1610 cm^{-1}

NMR (DMSO- d_6 , δ) : 3.75 (3H, s), 4.3-4.4 (2H, m), 4.97 (2H, s), 6.33-6.34 (1H, m), 6.83-6.87 (1H, m), 7.11-7.68 (14H, m), 8.38 (1H, s), 8.59 (1H, s)

Example 73

A mixture of N-(1-methylindol-5-yl)-N'-[3-(aminomethyl)phenyl]urea (500 mg), benzyl bromide (318 mg) and potassium carbonate (257 mg) in N,N-dimethylformamide (15 ml) was stirred at 100°C for 3 hours. This solution was partitioned between ethyl acetate and water. The organic layer was washed with water, dried over magnesium sulfate, filtered, and evaporated. The residue was chromatographed on silica gel (chloroform), triturated with ether to give N-(1-methylindol-5-yl)-N'-[3-(benzylaminomethyl)phenyl]urea.

mp : 119-123°C

IR (Nujol) : 1610 cm^{-1}

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NMR (DMSO-d₆, δ) : 3.66 (2H, s), 3.71 (2H, s), 3.75 (3H, s), 6.34 (1H, d, J=2.9Hz), 6.93 (1H, d, J=7.3Hz), 7.13-7.44 (12H, m), 7.70 (1H, s), 8.44 (1H, s), 8.59 (1H, s)

5 MASS : 385 (M+1)

Example 74

N-[3-(Benzylaminomethyl)phenyl]-N'-(benzo[b]furan-7-yl)-urea was prepared in a similar manner to that of Example 73.

10 mp : 78-82°C

IR (Nujol) : 1620 cm⁻¹

NMR (DMSO-d₆, δ) : 3.70 (2H, s), 3.73 (2H, s), 6.99-7.47 (12H, m), 7.96-8.05 (2H, m), 8.83 (1H, s), 9.15 (1H, s)

15 MASS : 372 (M+1)

Example 75

N-[3-(Benzylaminomethyl)phenyl]-N'-(2,3-dihydrobenzo[b]furan-7-yl)urea hydrochloride was prepared in a similar manner to that of Example 73.

20 mp : 106-112°C

NMR (DMSO-d₆, δ) : 3.22 (2H, t, J=8.6Hz), 4.09-4.15 (4H, m), 4.59 (2H, t, J=8.6Hz), 6.72-6.89 (2H, m), 7.17 (1H, d, J=7.4Hz), 7.29-7.64 (8H, m), 7.82 (1H, d, J=7.7Hz), 8.37 (1H, s), 9.54 (1H, s), 9.75 (2H, s)

25 MASS : 387 (M+1)

Example 76

30 N-(1-Methylindol-5-yl)-N'-[3-[(2-fluorobenzylamino)-methyl]phenyl]urea was prepared in a similar manner to that of Example 73.

mp : 109-112°C

IR (Nujol) : 1610, 1540 cm⁻¹

35 NMR (DMSO-d₆, δ) : 3.69 (4H, s), 3.75 (3H, s), 6.34

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(1H, d, J=2.9Hz), 6.93 (1H, d, J=7.4Hz), 7.11-7.55
(11H, m), 7.68 (1H, s), 8.41 (1H, s), 8.55 (1H, s)

MASS : 403 (M+1)

5 Example 77

N-(1-Methylindol-5-yl)-N'-[3-[(3-chlorobenzylamino)-methyl]phenyl]urea was prepared in a similar manner to that of Example 73.

mp : 124-125°C

10 IR (Nujol) : 1610, 1540 cm⁻¹

NMR (DMSO-d₆, δ) : 2.75 (1H, s), 3.65 (2H, s), 3.70
(2H, s), 3.75 (3H, s), 6.34 (1H, d, J=2.8Hz), 6.92
(1H, d, J=7.4Hz), 7.12-7.45 (11H, m), 7.70 (1H, d,
J=1.7Hz), 8.40 (1H, s), 8.55 (1H, s)

15 MASS : 419 (M+1)

Example 78

N-(1-Methylindol-5-yl)-N'-[3-[(2-chlorobenzylamino)-methyl]phenyl]urea was prepared in a similar manner to that of Example 73.

mp : 126-136°C

IR (Nujol) : 1610, 1540 cm⁻¹

20 NMR (DMSO-d₆, δ) : 2.69 (1H, s), 3.71 (2H, s), 3.75
(3H, s), 3.78 (2H, s), 6.34 (1H, d, J=2.8Hz), 6.95
25 (1H, d, J=7.3Hz), 7.12-7.44 (9H, m), 7.59 (1H, d,
J=6.2Hz), 7.69 (1H, s), 8.40 (1H, s), 8.54 (1H, s)

MASS : 419 (M+1)

Example 79

30 N-(1-Methylindol-5-yl)-N'-[3-[(4-chlorobenzylamino)-methyl]phenyl]urea was prepared in a similar manner to that of Example 73.

mp : 114-119°C

IR (Nujol) : 1610 cm⁻¹

35 NMR (DMSO-d₆, δ) : 3.64 (2H, s), 3.68 (2H, s), 3.75

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(3H, s), 6.34 (1H, d, J=2.9Hz), 7.34 (1H, d, J=7.3Hz), 7.12-7.43 (11H, m), 7.68 (1H, s), 8.40 (1H, s), 8.54 (1H, s)

MASS : 419 (M+1)

5

Example 80

N-(1-Methylindol-5-yl)-N'-[3-[(4-chlorobenzylamino)-methyl]phenyl]urea was prepared in a similar manner to that of Example 73.

10

mp : 141-144°C

IR (Nujol) : 1610, 1540 cm⁻¹

NMR (DMSO-d₆, δ) : 3.66 (2H, s), 3.69 (2H, s), 3.75 (3H, s), 6.34 (1H, d, J=2.6Hz), 6.93 (1H, d, J=7.6Hz), 7.10-7.44 (11H, m), 7.69 (1H, s), 8.44 (1H, s), 8.58 (1H, s)

15

MASS : 403 (M+1)

Example 81

N-(1-Methylindol-5-yl)-N'-[3-[(3,5-dichlorobenzylamino)-methyl]phenyl]urea was prepared in a similar manner to that of Example 73.

20

mp : 155-159°C

IR (Nujol) : 1610, 1570 cm⁻¹

NMR (DMSO-d₆, δ) : 2.87 (1H, s), 3.64 (2H, s), 3.70 (2H, s), 3.75 (3H, s), 6.33 (1H, d, J=2.8Hz), 6.97 (1H, d, J=7.3Hz), 7.13-7.44 (9H, m), 7.71 (1H, s), 8.41 (1H, s), 8.55 (1H, s)

25

MASS : 453 (M)

Example 82

N-(1-Methylindol-5-yl)-N'-[3-[(N-methyl-N-benzylamino)-methyl]phenyl]urea was prepared in a similar manner to that of Example 73.

30

mp : 78-80°C

35

IR (Nujol) : 1610, 1540 cm⁻¹

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NMR (DMSO-d₆, δ) : 2.10 (3H, s), 3.46 (2H, s), 3.50
(2H, s), 3.76 (3H, s), 6.34 (1H, d, J=2.9Hz), 6.92
(1H, d, J=7.4Hz), 7.13-7.70 (12H, m), 8.61 (1H, s),
8.77 (1H, s)

5 MASS : 399 (M+1)

Example 83

N-(4-(Dibenzylaminomethyl)phenyl)-N'-[1-methylindol-5-
yl]urea was prepared in a similar manner to that of Example
10 73.

mp : 181-183°C

IR (Nujol) : 1640 cm⁻¹

NMR (DMSO-d₆, δ) : 3.44 (2H, s), 3.49 (4H, s), 3.75
(3H, s), 6.33 (2H, d, J=3Hz), 7.13 (1H, dd, J=9Hz,
15 2Hz), 7.20-7.50 (16H, m), 7.68 (1H, d, J=2Hz), 8.41
(1H, br s), 8.54 (1H, br s)

MASS : 475 (M+1[⊕])

Example 84

To a suspension of N-[4-(aminomethyl)phenyl]-N'-[1-
20 methylindol-5-yl]urea (0.15 g) in toluene (5 ml) was added
benzaldehyde (0.052 ml). The mixture was refluxed under
nitrogen atmosphere for 4 hours. After evaporation, the
residue was suspended in ethanol (15 ml), and sodium
borohydride (57.9 mg) was added. The mixture was stirred at
25 50°C for 2 hours. After evaporation, the residue was
partitioned between water and chloroform. The chloroform
layer was dried over sodium sulfate, and chromatographed on
silica gel eluted by chloroform-methanol (0-5%, V/V) to give
N-[4-(benzylaminomethyl)phenyl]-N'-[1-methylindol-5-yl]urea
30 (0.11 g).

mp : 125-130°C

IR (Nujol) : 1640 cm⁻¹

NMR (DMSO-d₆, δ) : 3.62 (2H, s), 3.68 (2H, s), 3.75
(3H, s), 6.33 (1H, d, J=3Hz), 7.10-7.45 (12H, m),
35 7.68 (1H, d, J=2Hz), 8.40 (1H, br s), 8.51 (1H,

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br s)
MASS : 385 (M+1[⊕]), 278 (M-phCH₂NH[⊕])

Example 85

5 N-(1-Methylindol-5-yl)-N'-[3-[(2,6-dimethoxybenzyl)-aminomethyl]phenyl]urea was prepared in a similar manner to that of Example 84.

mp : 168-171°C

IR (Nujol) : 1610, 1590, 1540 cm⁻¹

10 NMR (DMSO-d₆, δ) : 3.34 (4H, s), 3.75 (3H, s), 3.77 (7H, s), 6.34 (1H, d, J=2.9Hz), 6.64 (1H, s), 6.68 (1H, s), 6.87 (1H, d, J=7.4Hz), 7.12-7.31 (6H, m), 7.47 (1H, s), 7.69 (1H, d, J=1.7Hz), 8.50 (1H, s), 8.64 (1H, s)

MASS : 445 (M+1)

15

Example 86

N-(1-Methylindol-5-yl)-N'-[3-(3-pyridylmethylaminomethyl)phenyl]urea was prepared in a similar manner to that of Example 84.

20 mp : 115-122°C

IR (Nujol) : 1650, 1600, 1540 cm⁻¹

25 NMR (DMSO-d₆, δ) : 2.84 (1H, s), 3.66 (2H, s), 3.71 (2H, s), 3.75 (3H, s), 6.34 (1H, d, J=2.9Hz), 6.93 (1H, d, J=7.3Hz), 7.13-7.44 (7H, m), 7.70-7.80 (2H, m), 8.41-8.55 (4H, m)

MASS : 386 (M+1)

Example 87

30 N-(1-Methylindol-5-yl)-N'-[3-[(2,5-difluorobenzyl)-aminomethyl]phenyl]urea was prepared in a similar manner to that of Example 84.

mp : 121-130°C

IR (Nujol) : 1610, 1540 cm⁻¹

35 NMR (DMSO-d₆, δ) : 2.72 (1H, s), 3.68 (2H, s), 3.72 (2H, s), 3.75 (3H, s), 6.34 (1H, d, J=2.9Hz), 6.93

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(1H, d, J=7.4Hz), 7.12-7.44 (9H, m), 7.69 (1H, s),
8.40 (1H, s), 8.55 (1H, s)

MASS : 421 (M+1)

5 Example 88

N-(1-Methylindol-5-yl)-N'-[3-[(2-methoxybenzyl)-aminomethyl]phenyl]urea was prepared in a similar manner to that of Example 84.

mp : 124-140°C

10 IR (Nujol) : 1610, 1540 cm⁻¹

NMR (DMSO-d₆, δ) : 3.68-3.69 (4H, m), 3.75 (3H, s),
3.77 (3H, s), 6.33 (1H, d, J=2.9Hz), 6.89-6.98 (3H,
m), 7.12-7.45 (8H, m), 7.69 (1H, d, J=1.7Hz), 8.42
(1H, s), 8.57 (1H, s)

15 MASS : 415 (M+1)

Example 89

N-(1-Methylindol-5-yl)-N'-[3-[(1-naphthyl)-methylaminomethyl]phenyl]urea was prepared in a similar
20 manner to that of Example 84.

mp : 74-78°C

IR (Nujol) : 1610, 1540 cm⁻¹

NMR (DMSO-d₆, δ) : 3.75 (3H, s), 3.79 (2H, s), 4.14
(2H, s), 6.34 (1H, d, J=2.8Hz), 6.98 (1H, d,
25 J=7.3Hz), 7.13-7.94 (14H, m), 8.10-8.20 (1H, m),
8.41 (1H, s), 8.56 (1H, s)

MASS : 435 (M+1)

Example 90

30 N-(1-Methylindol-5-yl)-N'-[3-[(2,4,6-trimethoxybenzyl)-aminomethyl]phenyl]urea was prepared in a similar manner to that of Example 84.

mp : 144-152°C

IR (Nujol) : 1700, 1610, 1540 cm⁻¹

35 NMR (DMSO-d₆, δ) : 3.76 (3H, s), 3.79 (9H, s), 3.88

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(2H, s), 3.96 (2H, s), 6.28 (2H, s), 6.33 (1H, d, J=2.8Hz), 7.05 (1H, d, J=7.7Hz), 7.16 (1H, d, J=8.6Hz), 7.28-7.40 (4H, m), 7.65 (1H, s), 7.71 (1H, s), 8.83 (1H, s), 8.99 (1H, s)

5 MASS : 475 (M+1)

Example 91

N-(1-Methylindol-5-yl)-N'-[3-[(2,4-dimethoxybenzyl)-aminomethyl]phenyl]urea was prepared in a similar manner to
10 that of Example 84.

mp : 108-111°C

IR (Nujol) : 1610, 1600, 1580, 1540 cm⁻¹

15 NMR (DMSO-d₆, δ) : 3.66 (2H, s), 3.72 (2H, s), 3.75-3.77 (9H, m), 6.34 (1H, d, J=3.0Hz), 6.47-6.55 (2H, m), 6.94 (1H, d, J=7.4Hz), 7.12-7.38 (7H, m), 7.45 (1H, s), 7.70 (1H, d, J=1.6Hz), 8.52 (1H, s), 8.67 (1H, s)

MASS : 445 (M+1)

20 Example 92

N-[3-(1-Benzylaminoethyl)phenyl]-N'-(1-methylindol-5-yl)urea was prepared in a similar manner to that of Example 84.

mp : 75-90°C

25 IR (Nujol) : 1640 cm⁻¹

NMR (DMSO-d₆, δ) : 1.27 (3H, d, J=7Hz), 3.40-3.80 (3H, m), 3.76 (3H, s), 6.34 (1H, d, J=3Hz), 6.95 (1H, d, J=7Hz), 7.10-7.50 (12H), 7.69 (1H, d, J=2Hz), 8.39 (1H, s), 8.55 (1H, s)

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Example 93

N-(Benzo[b]furan-5-yl)-N'-[3-(benzylaminomethyl)-phenyl]urea was prepared in a similar manner to that of
Example 84.

35 mp : 130-131°C

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IR (Nujol) : 1620, 3260 cm^{-1}

NMR (DMSO- d_6 , δ) : 3.68 (2H, s), 3.72 (2H, s), 6.90-
6.97 (2H, m), 7.18-7.51 (10H, m), 7.84 (1H, d,
J=2.0Hz), 7.93 (1H, d, J=2.2Hz), 8.64-8.65 (2H, m)

5 MASS : 372 (M+1)

Example 94

10 N-(Benzo[b]furan-5-yl)-N'-[3-[(2,4,6-trimethoxybenzyl)-
aminomethyl]phenyl]urea acetate was prepared in a similar
manner to that of Example 84.

mp : 95-110°C

IR (Nujol) : 1660 cm^{-1}

15 NMR (DMSO- d_6 , δ) : 3.78-3.89 (13H, m), 6.27 (1H, s),
6.90 (1H, s), 7.03 (1H, d, J=8.0Hz), 7.26-7.60 (5H,
m), 7.84 (1H, s), 7.93 (1H, d, J=2.1Hz), 8.98 (1H,
d, J=6.3Hz)

MASS : 462 (M+1)

Example 95

20 N-[3-[(3,4-Dimethoxybenzyl)aminomethyl]phenyl]-N'-(1-
methylindol-5-yl)urea was prepared in a similar manner to
that of Example 84.

mp : 100-110°C

IR (Nujol) : 1640 cm^{-1}

25 NMR (DMSO- d_6 , δ) : 3.67 (3H, s), 3.73 (4H, s), 3.75
(6H, s), 6.33 (1H, d, J=2.9Hz), 6.88-7.00 (4H, m);
7.11-7.50 (6H, m), 7.68 (1H, s), 7.69 (1H, s), 8.45
(1H, s), 8.59 (1H, s)

MASS : 445 (M+1)

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Example 96

35 N-(1-Methylindol-5-yl)-N'-[3-[(2,4,6-trimethylbenzyl)-
aminomethyl]phenyl]urea was prepared in a similar manner to
that of Example 84.

mp : 178-179°C

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IR (Nujol) : 1635 cm^{-1}

NMR (DMSO- d_6 , δ) : 2.18 (3H, s), 2.26 (6H, s), 3.58 (2H, s), 3.73 (2H, s), 3.75 (3H, s), 6.33 (1H, d, $J=3.0\text{Hz}$), 6.78 (2H, s), 6.96 (1H, d, $J=7.4\text{Hz}$), 7.11-7.45 (7H, m), 7.68 (1H, d, $J=1.7\text{Hz}$), 8.52 (1H, s), 8.58 (1H, s)

MASS : 427 (M+1)

Example 97

N-(Benzo[b]furan-5-yl)-N'-[3-[(2,4,6-trimethylbenzyl)-aminomethyl]phenyl]urea was prepared in a similar manner to that of Example 84.

mp : 183-185°C

IR (Nujol) : 1635 cm^{-1}

NMR (DMSO- d_6 , δ) : 2.18 (3H, s), 2.26 (6H, s), 3.59 (2H, s), 3.75 (2H, s), 6.78 (2H, s), 6.90 (1H, t, $J=0.86\text{Hz}$), 6.99 (1H, d, $J=7.5\text{Hz}$), 7.18-7.52 (5H, m), 7.83 (1H, d, $J=2.0\text{Hz}$), 7.93 (1H, d, $J=2.2\text{Hz}$), 8.60 (1H, s), 8.63 (1H, s)

MASS : 414 (M+1)

Example 98

N-[3-[(3,4-Dihydroisoquinolin-1-yl)aminomethyl]phenyl]-N'-(1-methylindol-5-yl)urea hydroiodide was prepared in a similar manner to that of Example 66.

mp : 224-228°C

IR (Nujol) : 1600, 1630, 1675 cm^{-1}

NMR (DMSO- d_6 , δ) : 3.03 (2H, t, $J=6.4\text{Hz}$), 3.54 (2H, t, $J=6.7\text{Hz}$), 3.75 (3H, s), 4.66 (2H, s), 6.33 (1H, d, $J=2.9\text{Hz}$), 6.97 (1H, d, $J=7.1\text{Hz}$), 7.13 (1H, dd, $J=8.7\text{Hz}$, 1.9Hz), 7.26-7.74 (9H, m), 8.06 (1H, d, $J=7.7\text{Hz}$), 8.46 (1H, s), 8.68 (1H, s), 9.90 (2H, s)

MASS : 424 (M+1)

Example 99

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N-[3-[[(Methylimino) (phenyl)methyl]aminomethyl]phenyl]-N'-(1-methylindol-5-yl)urea was prepared in a similar manner to that of Example 66.

mp : 138-152°C

5 IR (Nujol) : 1640 cm⁻¹

NMR (DMSO-d₆, δ) : mixture of tautomers, [major, 3.07 (3H, s), 4.36 (2H, s)], [minor, 2.82 (2H, s), 4.62 (2H, s)], [both, 3.76 (3H, s), 6.34-6.35 (1H, m), 6.75-6.79 (1H, m), 7.00-7.68 (14H, m), 8.48-8.51 (1H, m), 8.64-8.71 (1H, m), 9.6-9.8 (1H, m)]

10 MASS : 412 (M+1)

Example 100

N-(Benzo[b]furan-7-yl)-N'-(3-cyanophenyl)urea was prepared in a similar manner to that of Example 1.

mp : 208-215°C (MeOH)

IR (Nujol) : 3300, 2240, 1640, 1610, 1560 cm⁻¹

NMR (DMSO-d₆, δ) : 7.00 (1H, d, J=2Hz), 7.19 (1H, t, J=8Hz), 7.31 (1H, d, J=7Hz), 7.48 (2H, m), 7.68 (1H, d, J=9Hz), 7.94 (1H, d, J=7Hz), 8.04 (2H, m), 8.99 (1H, s), 9.46 (1H, s)

Example 101

N-(Benzo[b]furan-7-yl)-N'-(3-thiocarbamoylphenyl)urea was prepared in a similar manner to that of Example 2.

mp : 155-164°C

IR (Nujol) : 3270, 1630, 1600, 1555 cm⁻¹

NMR (DMSO-d₆, δ) : 7.00 (1H, d, J=2Hz), 7.14-7.46 (4H, m), 7.75 (1H, m), 7.98-8.08 (2H, m), 8.60 (1H, s), 9.35 (1H, s), 9.51 (1H, s), 9.89 (1H, s)

Example 102

N-(Benzo[b]furan-7-yl)-N'-[3-[methylthio(imino)methyl]phenyl]urea hydroiodide was prepared in a similar manner to that of Example 3.

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mp : 180-182°C

IR (Nujol) : 3400, 3170, 1680, 1625, 1550 cm⁻¹

NMR (DMSO-d₆, δ) : 2.86 (3H, s), 7.00 (1H, d, J=2Hz),
7.20 (1H, t, J=8Hz), 7.32 (1H, d, J=7Hz), 7.46 (1H,
5 d, J=8Hz), 7.60 (1H, t, J=8Hz), 7.70 (1H, d,
J=8Hz), 7.94 (1H, d, J=8Hz), 8.08 (1H, d, J=2Hz),
8.20 (1H, m), 8.94 (2H, s), 9.56 (1H, s)

Example 103

10 N-(Benzo[b]furan-7-yl)-N'-[3-(phenylamidino)phenyl]urea
was prepared in a similar manner to that of Example 6.

mp : 190-200°C

IR (Nujol) : 3200, 1675, 1650, 1625, 1590, 1540 cm⁻¹

15 NMR (DMSO-d₆, δ) : 7.01 (1H, d, J=2Hz), 7.19 (1H, t,
J=8Hz), 7.32 (1H, d, J=7Hz), 7.40-7.80 (8H, m),
7.96 (1H, d, J=7Hz), 8.08 (1H, d, J=2Hz), 8.14 (2H,
m), 9.00 (2H, m), 9.51 (1H, s)

Example 104

20 N-(1-Methylindol-5-yl)-N'-[3-[(2-thienylmethyl)-
aminomethyl]phenyl]urea was prepared in a similar manner to
that of Example 84.

Example 105

25 N-(1-Methylindol-5-yl)-N'-[3-[[3-
trifluoromethoxyphenyl)methyl]aminomethyl]phenyl]urea was
prepared in a similar manner to that of Example 84.

Example 106

30 N-[3-[[3-Methoxyphenyl)methyl]aminomethyl]phenyl]-
N'-(1-methylindol-5-yl)urea was prepared in a similar manner
to that of Example 84.

Example 107

35 N-[3-[[2-Methoxy-5-trifluoromethoxyphenyl)methyl]-

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aminomethyl]phenyl]-N'-(1-methylindol-5-yl)urea was prepared in a similar manner to that of Example 84.

Example 108

5 N-(1-Methylindol-5-yl)-N'-[3-(phenethylaminomethyl)-phenyl]urea was prepared in a similar manner to that of Example 84.

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